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Preponderance of Evidence Favoring Dextri-Maltose

Continued down from 1911

1920

"There are three sugars commonly employed in infant feeding: (1) malt sugar or dextri-maltose, (2) cane sugar, and (3) milk sugar. Malt sugar is the most easily digested and assimilated, cane sugar next and sugar of milk the least so."—*L. O. Frech: The caloric method of artificial feeding in normal babies, Illinois M. J. 38:484-488, Dec. 1920.*

1920

Regarding treatment in disturbed metabolic balance in infants, "The one carbohydrate which seems to give the most satisfactory results in these cases is malt sugar."—*C. H. Seybert: Disturbed metabolic balance in infancy, Hahneman. Monthly, pp. 379-382, June, 1920.*

1921

"Next to woman's milk is cow's milk in simple modification with water and sugar in proper proportions and amount according to the age of the child. Milk Sugar is the most expensive and least satisfactory sugar. Dextri-Maltose is the best sugar."—*A. A. Shawkey: Infant foods and infant feeding, West Virginia M. J. 15:284-287, Feb. 1921.*

1921

With reference to hypotrophy, "In mild cases, the addition of dextrimaltose instead of cane or milk sugar may be sufficient to obtain a gain in weight."—*C. Herrman: The treatment of nutritional disorders in artificially fed infants, New York M. J. 114:158-160, Aug. 1921.*

1921

"Maltose and dextrin compounds are acceptable to the infant's digestion in relatively larger quantities. They are not as sweet as cane sugar. They are of practical value when larger amounts of cane sugar are not well borne.

"The so-called 'Mead's Dextri maltose with Potassium Bicarbonate' is laxative, and in the presence of a stationary weight may be given in larger amounts."—*F. W. Fergusson: A method for the modification of cow's milk, Journal-Lancet, 41:628-629, Dec. 1, 1921.*

1921

For cases of fermentative diarrhea, ". . . the ideal plan of treatment would be to give a food which is low in sugar (the food which that group of organisms thrive on) and high in protein. Calcium caseinate milk accomplishes this purpose. In our series of cases, we found it was necessary to use the casein calcium for from 5-8 days; we then stopped it and added dextri-maltose to the formula."—*A. G. DeSanctis and L. V. Paider: The value of calcium caseinate milk in fermentative diarrhea, Arch. Pediat. 38:233-236, April, 1921.*

1922

"Lactose in reasonable amounts under normal conditions has a slight laxative action, as does maltose, while saccharose is slightly constipating. When given in excess, lactose is more likely than the other disaccharides to cause diarrhea, the order being lactose, saccharose, maltose and dextrin-maltose mixtures. The probable explanation of the greater frequency with which lactose causes diarrhea is its relatively slow absorbability."

"There can be no doubt, therefore, that under normal conditions the preferable sugar for the well infant is lactose. This is not the case, however, in many of the disturbances of digestion. Some of these are due to an excessive amount of milk sugar in the food. They can be quickly relieved by a reduction in the percentage of milk sugar. In others, while the disturbance is not due primarily to the amount of milk sugar, the chief cause of the symptoms is the fermentation of the milk sugar as the result of abnormal bacterial activity. In such instances the milk sugar must be stopped and some other form of sugar substituted for it."

"The properties of maltose and the dextrins are materially different. Maltose is a disaccharide, dextrins are polysaccharides. Maltose is a crystalloid, fermentable and dialyzable; the dextrins are reversible, protective colloids, non-fermentable and non-dialyzable. It is evident, then, that it is not a matter of little importance which of these preparations is used. All are, of course, eventually absorbed in the form of dextrose. The dextrins being protective colloids, in all probability have a favorable influence on the digestibility of the protein in the same way as does starch. Maltose has no such action. The dextrins have to be changed to maltose and then to dextrose before they are absorbed. The larger the proportion of dextrin in the dextrin-maltose mixtures, the slower, therefore, is the absorption of sugar and vice versa. There is, consequently, less danger of overtaxing the absorptive mechanism of the intestine and of flooding the organism with sugar when the proportion of the dextrins is relatively high. On the other hand, if it is desired to give the sugar in a form which can be very readily and rapidly absorbed, the proportion of maltose should be large."

"Maltose is split into dextrose and dextrose which can be immediately utilized. Lactose is split into dextrose and galactose, and saccharose into dextrose and levulose. Only the dextrose half of these sugars is, therefore, immediately available without further change. This immediate availability of the whole of the malt sugar is presumably of some advantage in feeble, emaciated babies, who have little or no reserve of glycogen in the liver, in that all of the energy derived from the sugar may be used immediately in the digestion of the rest of the food, whereas the energy of the other sugars is not at once utilizable, the galactose and levulose halves having to be converted into glycogen in the liver and then reconverted into maltose and dextrose. The net energy value of malt sugar is also presumably somewhat greater than that of lactose and saccharose, because the sugar being converted at once into dextrose, no further energy is required, as there is to convert the galactose and levulose. The immediate utilizability of malt sugar is the chief point in favor of the employment of this form of sugar in the feeding of babies not suffering from disturbances of the digestion. This fact, while of importance in the feeding of feeble and emaciated babies, who have but little or no reserve of glycogen in the liver, is of no advantage in the feeding of normal infants. In fact, it is probably somewhat of a disadvantage. Milk sugar which is more slowly broken up and more slowly stored in the liver in the form of glycogen, is more suitable, in that it is less likely to overtax the liver and cause alimentary glycosuria and excessive fat production."

"There is a form of indigestion, chiefly intestinal, in infancy due to the fermentation of milk sugar. In the convalescent stage of this condition the dextrin-maltose preparations can be given sooner than lactose without causing a return of the symptoms. Their use is, therefore, indicated in this condition. The preparations containing a relatively large proportion of dextrins are preferable, because they are broken down more slowly."

"Attention has recently been called to the use of 'polycarbohydrates' in infant feeding. Those who use this term mean by it a combination of several carbohydrates in the same food. They believe that, on account of the difference in the rapidity of absorption of the different carbohydrates, more carbohydrate can be given in this way without overtaxing the power of the organism to assimilate and utilize sugar than when a single carbohydrate is used. This belief is unquestionably correct and there is no doubt that when there is a disturbance in the digestion of sugar it is of great advantage to give some of the carbohydrate in the form of starch. . . . The mixtures of milk, dextrin-maltose mixtures and simple cereal waters contain the carbohydrates in sufficient variety to meet the indications for the 'polycarbohydrates.' The malt sugar is absorbed first, then the milk sugar, next the dextrins and finally the starch. The absorption is thus comparatively slow and continues for a long time. The sudden flooding of the organism with sugar is thus avoided."—*J. L. Morse and F. B. Talbot: Diseases of Nutrition and Infant Feeding, Macmillan Co., New York, 1922, pp. 206, 207, 208, 209, 213.*

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The Journal of Pediatrics

VOL. 4 APRIL, 1934 NO. 4

Original Communications

THE RELATIONSHIP OF HOME AND HOSPITAL IN THE MANAGEMENT OF SICK CHILDREN

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THE Committee on Hospitals of the White House Conference, of which Dr. Grulee was chairman, calls attention in its foreword to the change that has taken place in the fundamental character of children's hospitals. "In any study of what is being done for the health and protection of children, the hospital at once stands out as a very important factor. Our ideas as to its functions in this field have changed very materially during the past twenty years. *It is no longer simply an asylum where the sick person may be treated for his or her physical ailments.*" (Author's italics.)

The original foundling institution was a theoretical haven of refuge for the abandoned infant. Society, moved by the pathetic scene, created a substitute for the home that should have sheltered its own young. Still moved by the same generous impulse, the hospital of the present day has responded to the spirit of the scientific age. Our operating rooms and laboratories exhibit the last word in equipment and scientific method. Undergoing this change, we are apt to maintain an interest in sick children as roentgenographs and biologic problems and lose sight of their human qualities, thinking of our patients as subjects of experiments in vitro and failing to realize that they are not in reality glass-enclosed problems but part of the homes from which they come and to which they go.

Our internes are particularly unresponsive to this phase of pediatrics. The average pediatric interne has a blind spot toward the social service report. The family history reading "F. and M. l. and w. 3 B. and 1 S. 1 and w." could not be decoded into an intelligible family background by S. S. Van Dine himself. It no more describes the Mexican family, one of whose members had tuberculosis of the bone, than the "Count

Presented before the Chicago Pediatric Society, October 17, 1933.

fours'' of the military squad identified its members. The laconic and stilted phraseology of the average clinical history is neither informative in its content nor does it possess the wit that brevity parades. The report of the British captain sent to govern a South African tribe was a mine of information in comparison. He was asked to record in his report a chapter on the customs and morals of the people. He wrote four words: ''Customs, beastly. Morals, none.''

In our private practice, our therapy is varied and relates itself to a particular home situation. Ingeniously, we blend scientific procedure with human understanding. The paradox is all the more surprising, that in our hospital work we delegate the study of the home to a social worker whose report we proceed to treat with disinterested remoteness.

More grievous still is the notion handed down from one interne staff to another that every sick child belongs to the hospital, and that the home is incapable of handling the sick child. This fallacy is reflected in the attitude taken by internes when a child is taken home before it has been officially discharged. The phrase ''Discharged against advice'' with all its implications characterizes a practice that is regarded as almost the worst kind of *lèse majesté*.

H. G. Wells in ''The New Machiavelli'' described a character as having the temperament that would cut down trees and put sanitary glass lamp shades in their stand—and something of this spirit seems to direct us in our attitude to the relationship of institution and home in pediatrics. For purposes of illustration, I would like to submit a characteristic case history.

D. S., an eighteen-month-old infant, is admitted to the Milwaukee Children's Hospital with an unexplained fever and cough of some duration. A roentgenogram, tuberculin test, and physical examination establish the diagnosis as tuberculous bronchopneumonia. The child lies listlessly in his crib, coughs occasionally, continues to run an irregular fever. He is given cod liver oil, and all that a hospital can give, but he does not seem to respond. The mother is unintelligent, noisy, dowdy. The father helped win the war, was gassed and draws a small pension. He is otherwise unemployed. The mother would like to take the child home. She lives in a shack on the outskirts of the city. She is willing to put the baby outdoors and follow instructions. The interne has a long argument with the mother, but the mother takes the child home against advice.

In the middle of July, this child was taken home. He was placed in a play pen, stripped. He gained weight, lost his fever, and when he came back to the out-patient department after two weeks showed a truly remarkable improvement. Since that time he has had a cervical adenitis, which he weathered equally well as an out-patient. The nursing follow-up on this patient had much to do with the cooperation obtained and the end-result achieved.

It so happened that this infant's home was a shack on the outskirts of the city. The shack, situated at the edge of town, had no other houses around it. Acres of ground, grass, and trees surrounded it. With proper social service and nursing follow-up, such a home was an ideal place for this infant, far superior in this instance to the well-ordered appointments of the hospital ward.

At the time this patient was being observed, we were experimenting with the plan of handling, as out-patients, a group of children that would ordinarily have been hospitalized. This program involved no great departure from any children's hospital's ordinary routine. It attempted a more intensive home follow-up, using the Speedwell program as the ideal. It differed from the Speedwell plan in that instead of foster homes we utilized the patient's own home in the majority of instances. It attempted to project the usefulness of the hospital into the home and enlarge the function of the hospital by the home education resulting from the nurse's visits. The primary reason for our interest in the plan was the experience of a distressingly high mortality rate among certain groups of infants.

I will not take your time longer than to mention that from your own group have come some of the most valuable contributions to this idea, that hospitalization of infants may not always be the happiest solution for the sick infant. Read Abt, talking before the Children's Hospital Association in 1925, regarding the dangers of massing infants in hospitals and his practical suggestion, "Keeping those babies at home where conditions permit them to remain at home." Read Brennemann, speaking before the American Pediatric Society: "No patient should be admitted to an infant ward who can with reasonable assurance be taken care of in an out-patient department, or in a good home, or foster home. Our own infant wards of thirty beds in a 285-bed hospital are rarely full, often only half full, and at times get down to six or seven patients. Only about 10 per cent of our patients are under eighteen months of age. Especially to be excluded are boarders and infants with infections of the respiratory tract and gastrointestinal disorders that are not immediately serious. . . ." If you would be stirred, read Jacobi, like a gladiator making his last stand before the lions, in the "Nursery and Child's Hospital" episode of his Collectanea. The same tone of conviction you will find in Chapin writing of the Speedwell, though not keyed to such a pitch.

"Progress," said Sir Clifford Allbutt in his delightful talk on Professional Education, "consists not only in anticipation of new ideas but also in timely apprehension of the passing of them, and a readiness to shed them betimes, not catastrophically but as a growing tree sheds its leaves. Otherwise we lose sight of their main form . . . we muddle on

and finding ourselves houseless, know not how to rebuild, how to convert old materials to new needs."

The analogy is not a perfect one, because as far as materials go, our institutions are conspicuously new. In the use of these new technics, we have spared neither cost nor effort to make them available for every sick child. Our confusion derives from the fact that in our clinical enthusiasm we become so interested in the case that we forget the larger implications of our medical tradition—that medicine was human before it was scientific.

The new need then demands neither new tools nor technique. It merely calls for the application of those principles that we utilize every day in our private practice. More than any one thing, we need to modify our conception of the relationship of home and hospital. The institution cannot exist as an isolated agency. Whatever remedial work it does must not be done merely for today but must relate itself to the whole child. Caring for the infant without teaching the mother how to do it is like Sisyphus, forever rolling up the mountain the stone that keeps rolling back. However inspired its motives, the institution whose program does not include the home misses a most important function—that of education.

If the hospital for children is to maintain its position as a health agency in the community, it must possess a more dynamic relationship to the family than is afforded by the polite contacts of nurse, interne and parent in the hospital ward.

To achieve this relationship, we should do well to accept the suggestion made to other social agencies by Mary Richmond. "The one practical suggestion that I can make to you," she said, "is that you ransack all your work for a year say, from top to bottom with reference to its influence upon the particular families from which your beneficiaries have come and to which they go. Examine every admission to your institution and every discharge from it with reference to this central fact."

It means reinterpreting the purpose of the children's hospital in terms of present-day conditions—integrating its activities with those of every agency that deals with any phase of child health.

"May the hospital of the future," says Carpenter, "need fewer ward beds for sick children, and may these be chiefly used for children requiring special diagnostic procedures."

Carpenter suggests a department of preventive medicine in every children's hospital. The natural outgrowth of such a department would be from the out-patient department, utilizing already existing machinery necessary in its development. In the usual out-patient department, social service workers and nurses visit the home and record their findings. Such home visits should not be restricted to these workers. The resident or interne learning modern pediatrics could not put in a more useful serv-

ice than in one which actually requires his following patients into their homes.* This procedure, more than anything else, would develop the sociologic understanding so often missing among young pediatricians.

It is important for admitting internes to learn that the child with a case of simple diarrhea or sore throat is not necessarily a hospital case; that they learn to utilize the home for the sick infant or child whenever it is possible, keeping the responsibility of the child's care where it belongs; that they send any infant or child into the hospital only whenever a special technic unavailable in the home is indicated, and most important of all, that no matter how successful a hospital therapy may be, it cannot be permanent unless the home from which the child comes is prepared to follow the plan initiated in the hospital.

In summarizing the social trends of the past thirty years as related to childhood, Lawrence K. Marsh says, "The child welfare movement is being impeded by the rigidity of the organizations, the lack of real concern for the well-being of children they have under their care, and inability to correlate the several parts of the work into a coherent problem. . . . There is need for a rededication of these various agencies to the task of child welfare and a keener realization of their responsibilities to the whole child."

In treating the whole child, the children's hospital must project its interest outside its own physical walls and include the home from which the child comes. Sensitive to its original humanitarian purposes, it will enlarge their value by a technic that embraces the teachings of biology and sociology.

2018 East North Avenue

*Such a service has recently been inaugurated as part of the Newborn Service at the Rush Medical College, by Dr. Grulee.

ERYTHRODERMIA DESQUAMATIVA

LEWIS WEBB HILL, M.D.
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IN ANY large series of eczematous infants there are some whose skin condition is characterized by a diffuse and intense redness with scaling, sometimes with extensive exfoliation. This was first described by Leiner[1] in 1908, who gave it the name "erythrodermia desquamativa." Since then a good many reports of series of such cases have appeared in the German and in the Italian literature, but as far as I know the only discussion of it in the American literature is a brief paper in 1930 by Greenthal,[2] who reported one case. According to the German authors, it is a disease especially of breast-fed infants in the early months of life. In Leiner's original series of forty-three cases, forty-one were breast fed, in Wittmann's[3] fifty-six of seventy-four, and in Moro's[4] one hundred and four of one hundred and thirty-four. The mortality rate is high, according to most authors from 16 to 50 per cent, although Schoenfeld[5] in a recent report had a mortality rate of only 7 per cent. Diarrhea is common, and nutrition is likely to be poor.

Most of the German and Italian authors admit they know nothing of its etiology. Moro, however, believes that it is caused by lack of a special vitamin, which he calls the "H vitamin," in combination with a relatively high intake of fat in the breast milk. The reason that the disease is more common in breast- than in bottle-fed infants, is, he believes, that breast milk contains less of the vitamin, or "minimal substance" as he calls it, than does cow's milk. There is no uniformity of opinion as regards treatment. Moro regards the addition of cow's milk, liver, and carrot juice to the diet, as specific, for they contain relatively large amounts of vitamin H. Schiff,[6] however, says that "through no form of vitamin therapy is it possible to do any good whatever to an erythrodermic child." One author recommends repeated small transfusions, another autohemotherapy; another, pituitary injections. Wittmann[3] says that there are too many methods of treatment for any of them to be of specific value, and admits he knows nothing about it. Hirsch,[7] likewise, admits he knows nothing whatever of etiology and says that time is the most important factor in cure.

From this brief review it is evident that erythrodermia desquamativa is a fairly common condition in Germany, that varying modes of treatment have been recommended, and that very little is known of its etiology.

From the Eczema Clinic, Children's Hospital, and the Department of Pediatrics, Harvard Medical School.

It is undoubtedly less common here than there, and it also differs, as it occurs here, in certain respects from the German descriptions.

In a series of approximately 800 cases of "infantile eczema," I have seen only twenty-one which fit into the erythrodermia group. The appearance of the skin is quite characteristic, and diagnosis is not difficult in a typical case. The entire skin surface is very red, never very dry, possibly somewhat moist in spots, but rarely with much oozing, and

Fig. 1.—Erythrodermia, good nutrition.

Fig. 2.—Erythodermia, poor nutrition. Note scaling on cheeks and enlarged lymph nodes in groin.

consequently little crusting (Fig. 1). In some cases there may be almost no scaling, and the skin may be simply fiery red all over, with otherwise a fairly normal appearance; in others there may be a fine branny desquamation. There is usually considerable scaling, however, and sometimes extensive exfoliation. The scalp is almost always covered with yellowish scales and crusts. One thing that I have not seen mentioned by other authors is blueness of the hands and feet. In twelve of our patients this was present. They were very cold, blue, and clammy;

and as the infant began to get better, if he did get better, this disappeared. The nutrition in my patients varied; some were practically athreptic, others in an excellent state of nutrition (Fig. 2).

According to many dermatologists, if one wishes to make a narrow definition of eczema, it is that in true eczema there are always vesicles, or at any rate papulovesicles. Vesiculation is absent in erythrodermia, and the skin is smooth as a rule. In some cases the entire body is not red, but perhaps only the feet, legs, and buttocks, as far as the waist; or sometimes the redness may be of a patchy character, occurring in large or small maculopapules, which soon coalesce.

This is definitely a disease of early life; eleven of my cases began before the end of the second month; one only as late as the sixth month. Only three were breast fed when the disease began; the others were on ordinary milk mixtures, and in practically every case the feeding had

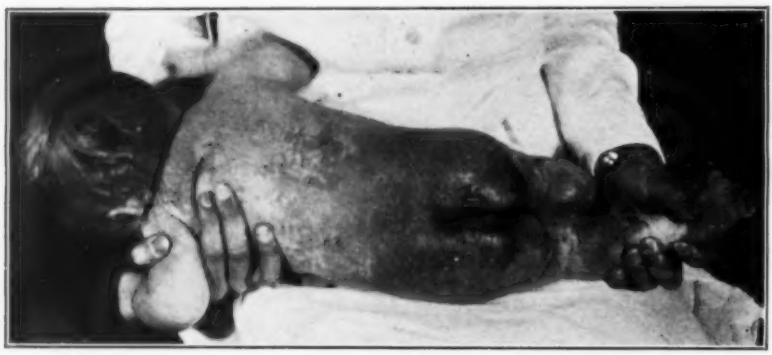

Fig. 3.—Patient A. S. Partial erythrodermia. Before treatment.

been a reasonable one, such as any capable pediatrician would give to a baby. In two cases diarrhea was a prominent symptom; in the others the bowel movements were normal. In six the disease began when the baby was weaned from the breast to the bottle. Two patients died, a mortality rate of about 9 per cent. They died with what was apparently severe general infection, localized in the respiratory tract. Several others developed respiratory infections; these babies are very susceptible to such infection and do not stand it well.

It is not easy to make skin tests on these patients, for frequently the skin is in such a condition that practically no normal skin is available. Skin tests were made in fourteen cases; six gave positive reactions. Four gave reactions to egg and to nothing else; one to wheat and tomato; one to wheat and chicken. In no case was there a reaction to anything that the child had eaten or was eating. There were no positive reactions to milk.

It is evident that this disorder is of systemic origin, and that no local treatment will cure it. After trying various washes and salves, I have come to the conclusion that there is nothing any better than boric ointment. This tends to prevent infection and to remove scales. Crude coal tar is contraindicated almost always; it is too strong, inasmuch as there is ordinarily little infiltration of the skin.

The basic process in erythrodermia desquamativa appears to be a dilatation of the small cutaneous vessels, and the most reasonable assumption is that this is brought about in some way from the digestive

Fig. 4.—Patient A. S. Partial erythrodermia. Before treatment.

tract. For this reason I have tried various diets, but with very little preconceived idea as to what might prove of value. Evaporated milk and Similac were used in several cases because of their easily digested protein. No results were noted. Three patients were given liver juice and carrot juice for the vitamin H which they are supposed to contain. This feeding had no effect. Seven patients were given a milk-free diet relatively low in fat and carbohydrate and high in protein; four of these were cured, one in a week, the others in about a month. In the three other cases the milk-free diet had no effect. One case was cured by weaning from the breast to a cow's milk formula. The most recent type of feeding that I have used, following the suggestion of György[8]

is a cow's milk formula relatively low in fat and carbohydrate and high in protein. This is made of partially skimmed milk, added carbohydrate, and five level tablespoonfuls of powdered casein to the quart. This has been used to date in six cases. Four were cured in from four to six weeks; one is at the present greatly improved; and one is not at all improved after two months of this feeding. I should not be willing to

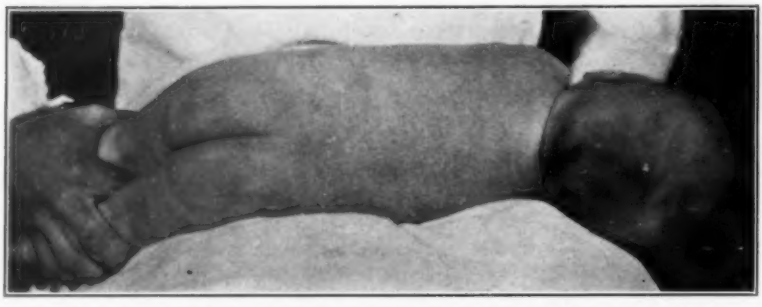

Fig. 5.—Patient A. S. After three weeks of low fat and high protein diet.

Fig. 6.—Patient A. S. After three weeks of low fat and high protein diet.

say that this method of feeding is a specific cure, but it has given the most consistently good results of any I have yet tried, particularly in cases of partial erythrodermia (Figs. 3, 4, 5 and 6). The milk-free diet, which was successful in four cases, is also low in fat and carbohydrate and high in protein, and it is likely that this is the reason it was successful, rather than that the patients were sensitized to cow's milk.

Where does this condition belong in classification? The Heidelberg school (Moro and György) believes that it is a greatly intensified

seborrheic dermatitis; this is probably correct, for all gradations may be seen, and there are practically always well-defined seborrheic scales. The relationship between seborrheic dermatitis and eczema in infancy is not at all clear, for in so many cases, one merges into the other. Seborrheic dermatitis is defined as an eruption which is characterized by more or less sharply circumscribed areas of dermatitis with seborrheic scaling. It occurs frequently during the early months of life and very often becomes eczematized, that is, vesiculated and thickened, when it is called seborrheic eczema. It is certainly in young infants often the precursor of true eczema; the infants who show a tendency to seborrheic manifestations in the second or third month are the ones who develop true eczema with positive skin tests at the sixth or seventh month so that most of the time it is not possible to make a clear distinction. In clean-cut cases the skin tests are likely to be negative, particularly in very young infants. As the baby grows older, they are more likely to be positive, consequently it would seem reasonable to look upon many cases of seborrheic dermatitis, although not in their clinical appearance characterized by the vesiculation of true eczema, as the first stage of eczema. If erythrodermia desquamativa is seborrheic dermatitis (and it seems likely that it is), they both bear the same relationship to eczema. I believe that they occur sometimes in allergic and sometimes in nonallergic children and that the particular way in which the skin reacts, that is, by diffuse redness and scaling, is determined by constitutional and nutritional factors of which we know but little. It seems well to look upon erythrodermia desquamativa not as a distinct disease, but rather as a symptom-complex occurring in certain seborrheic and eczematous infants, for it is not possible to give it an entirely clean-cut and sharply defined place in classification.

We are perhaps justified in drawing the conclusion that this particular symptom-complex is favored in its development by a diet relatively high in fat and sugar, and is retarded by a diet low in fat and sugar and high in protein. At present, I do not believe we can go further than this in any consideration of etiology.

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RICKETS IN RATS BY IRON FEEDING

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INTRODUCTION

THE studies reported here were undertaken in pursuance of some ideas arising out of preliminary experiments bearing upon the problem of the absorption of iron.[1] It was found that the dialysis of ferric ammonium citrate across cellophane membranes was markedly impeded by the addition to the solution of the secondary and tertiary sodium phosphates, even though there was no precipitate. This effect was considered to be due to the formation of colloidal ferric phosphate. Other soluble iron salts used in these dialysis experiments all formed precipitates with secondary and tertiary sodium phosphate under the conditions of the experiment, and the passage of the iron salts was naturally greatly impeded. The supposition that these principles might be applicable to conditions in the intestinal tract suggested the possibility that iron and phosphorus might, by forming insoluble compounds in the intestinal tract, each hinder the absorption of the other.

It was decided, therefore, to find out whether in the case of rats the addition of iron to a nonrachitogenic diet might so interfere with the absorption of phosphorus as to render that diet rachitogenic.

EXPERIMENTAL

Young rats were obtained from the Albino Supply Company of Philadelphia. They were of the type called by the suppliers "vitamin rats," recently weaned, and weighing between 35 and 50 grams.

The rats were divided into groups of five to a cage, all being exposed to the same amount of daylight coming through a plain glass window facing north.

Particulars are given in Table I of the various diets used.

The Control Diet used is one which has repeatedly been shown to be nonrachitogenic to rats.

The Steenbock Rachitogenic Diet is a high calcium, low phosphorus diet, which has repeatedly been shown to be rachitogenic to rats under conditions similar to those which were used for our animals. *Each of the remaining diets consists of the control diet plus the various substances mentioned.*

From the Departments of Pediatrics and Medicine, Harvard Medical School, and the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital.

*Leeverhulme Research Scholar of the Royal College of Physicians, London.

TABLE I

TYPE OF DIET	INGREDIENTS IN GRAMS		Ca (GM.)	P (GM.)	RATIO Ca:P	ADDED Fe (GM.)	REMARKS
Control	Corn meal Wheat Gluten Sodium Chloride Calcium Carbonate Dibasic Sodium Phosphate (anhydrous)	760 200 10 30 16	12.4	6.0	2:1		
Steenbock Rachitogenic	Cornmeal Wheat Gluten Sodium Chloride Calcium Carbonate	760 200 10 30	12.4	2.5	5:1		Steenbock Rachitogenic Diet No. 2965
Ferric Chloride	Control Diet plus $FeCl_3.6H_2O$	44	12.4	6.0	2:1	9.14	9.14 gm. of Fe combine chemically as ferric phosphate with 5.06 gm. of phosphorus, or as ferrous phosphate with 3.37 gm. of phosphorus
Ferric Chloride and Added Phosphorus	Cornmeal Wheat Gluten NaCl $CaCO_3$ Na_2HPO_4 (anhydrous) $FeCl_3.6H_2O$	760 200 10 30 42.3 44				9.14	This diet contains 26.3 gm. of Na_2HPO_4 more than the control. This represents 5.07 gm. of phosphorus which is sufficient to combine chemically with the 9.14 gm. of iron as $FePO_4$
Ammonium Chloride	Control Diet plus NH_4Cl	26.4					26.4 gm. NH_4Cl contain the same weight of chlorine as 44 gm. of $FeCl_3.6H_2O$
Ferric Ammonium Citrate	Control Diet plus Ferric Ammonium Citrate	51				9.14	Same content of metallic iron as the Ferric Chloride Diet
Ferrous Chloride	Control Diet plus $FeCl_2$ (anhydrous)	19.3				8.6	Approximately same content of metallic iron as the Ferric Chloride Diet
Reduced Iron	Control Diet plus Ferrum Reductum (U.S.P.)	15					Approximately same content of metallic iron as the Ferric Chloride Diet
Organic Iron	Control Diet plus Ferric Glucamate	91.4					A proprietary organic iron preparation containing approximately 10% metallic iron

The Ferric Chloride Diet contains iron (9.14 gm.) sufficient to combine chemically as ferric phosphate with 5.06 gm. of phosphorus, or as ferrous phosphate with 3.37 grams of phosphorus. Iron in the above quantity was added to the control diet on the assumption that, by forming in the intestinal tract insoluble ferric or ferrous phosphate, it might interfere with the absorption of phosphorus.

The Ammonium Chloride Diet contains the same weight of chlorine as is contained in the ferric chloride present in the previous diet. It was intended to eliminate the possibility that any rachitogenic effect of added ferric chloride might be due to alterations in the hydrogen ion concentration of the contents of the intestinal tract or to the chlorine radical.

The Ferric Chloride and Added Phosphorus Diet contains in addition to the phosphorus already in the ferric chloride diet a further allowance of phosphorus, sufficient to combine as ferric phosphate with all the added iron, and thus provide the same amount of "unbound" phosphorus as the control diet.

The Ferric Ammonium Citrate, Ferrous Chloride, Reduced Iron, and Organic Iron Diets consist each of the control diet with the addition of the salt named, in amount sufficient to yield about the same weight of metallic iron as is contained in the ferric chloride diet.

The diets were made up in the following manner. Each of the salts was finely ground in a mortar and intimately mixed in a large bowl with dry corn meal and wheat gluten. The mixture, after the addition of sufficient water to make it cohesive, was rolled out upon a piece of smooth paper which had been greased with olive oil, cut into small sections, and baked until crisp in a oven. In the case of ferric chloride and ferric ammonium citrate, these salts were dissolved in the amount of water which had to be added to the mixture. Water and food *ad libitum* were supplied fresh each day.

The control diet and the ammonium chloride diet were very well taken and the rats gained weight well and remained sleek and healthy. The Steenbock rachitogenic diet, the ferric chloride diet, the ferric chloride with added phosphate diet, the ferric ammonium citrate diet, and the ferrous chloride diet were moderately well taken. The animals appeared in good health but gained little weight. The reduced iron diet was less well taken and the animals lost weight. The organic iron diet was obviously hard and unpalatable to the rats. Although the animals on this diet appeared to be in moderately good health, they lost a great deal of weight. In spite of loss of weight in the last two groups all the animals obviously increased in skeletal stature. There was no noticeable diminution of activity nor weakness of the extremities.

The rats were weighed individually at the start of the experiment, and again from time to time throughout the duration of the experiment. After ten days or a fortnight they were lightly anesthetized with ether and radiographed to detect the development of rickets.

At the termination of the experiment, the animals were anesthetized, decapitated and as much blood drained out of the body as possible. The blood from each group was pooled, and the serum phosphorus estimated by the method of Fiske and Subbarow.[2] Each carcass was then radio-

TABLE II

GROUP NO.	NO. OF RATS IN GROUP	DIET	NO. OF DAYS ON DIET	AVERAGE CHANGE IN WEIGHT (GM.)	POOLED BLOOD PHOSPHORUS (MG. %)	DEGREE OF RICKETS REPORTED BY ROENTGENOGRAM	DEGREE OF RICKETS REPORTED BY MICROSCOPIC STUDY OF SECTIONS
1	5	Control	22	+ 5.2	7.3	None	None
2	5	$FeCl_3$	22	+ 2.0	2.5	Advanced active	Severe active; quantitatively more severe than that seen in any of the other groups
3	5	NH_4Cl	22	+ 4.6	7.2	None	None
4	4	Steenbock	22	+ 1.75	3.7	Advanced active	Severe active
5	5	Control	26	+ 9.8	5.7	None	None
6	5	NH_4Cl	27	+10.6	7.8	None	None
7	4	Steenbock	27	+ 4.0	2.6	Advanced active	Severe active
8	5	$FeCl_3$ + added P	27	- 0.5	6.2	None	None
9	5	Fe Am. Citr.	27	- 1.8	3.8	Mod. advanced active	Mod. severe active; less than $FeCl_3$
10	5	Fe_2Cl_3	26	+ 0.4	2.7	Mod. advanced active	Mod. severe active; less than $FeCl_3$
11	4	Fe Reduct.	26	- 4.0	3.6	None	Active, mod. severe
12	4	Organic	26	-12.75	5.6	None	None

graphed. One knee joint and two or three costochondral junctions were taken from each animal for microscopic examination. Sections were made from the principal organs of the body to determine if there was evidence of disease.

RESULTS

The results of these experiments are summarized in Table II. The first four groups in the table comprise the preliminary experiment in which the effect of added iron in the form of ferric chloride was studied. The five rats on the control diet showed no rickets in twenty-two days, whereas the four rats on the Steenbock rachitogenic diet all showed gross manifestations of rickets at the end of the same period of time. The

Fig. 1.—Control diet; no rickets; section of costochondral junction (×104).

five rats fed on the ferric chloride diet all presented the manifestations of rickets to a degree at least as marked as those on the Steenbock rachitogenic diet. None of the rats fed on the ammonium chloride diet showed any manifestations of rickets.

Groups 5, 6, and 7 were repetitions of Groups 1, 3, and 4, respectively, and confirmed the results previously obtained with the control diet, the Steenbock rachitogenic diet, and the ammonium chloride diet.

Group 8 was fed on a diet which contained ferric chloride in an amount which has been shown in Group 2 to produce rickets. But in this case the ferric chloride was "covered" by an amount of added phosphate sufficient chemically to combine with all the iron as ferric phosphate. None of these rats showed any manifestations of rickets.

Groups 9 and 10 were fed on a diet to which had been added, respectively, ferric ammonium citrate and ferrous chloride in amounts equiva-

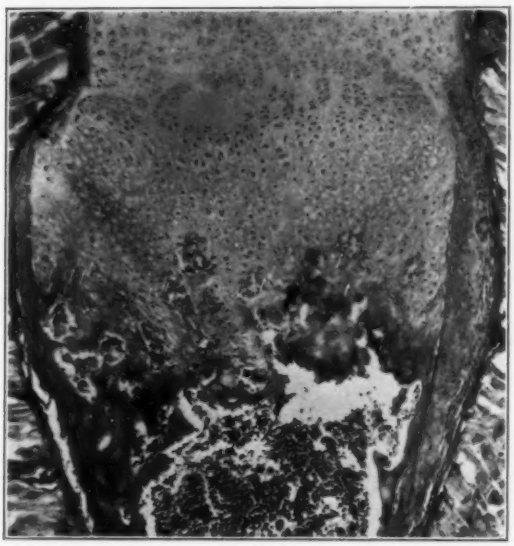

Fig. 2.—Steenbock rachitogenic diet; active rickets; section of costochondral junction (×104).

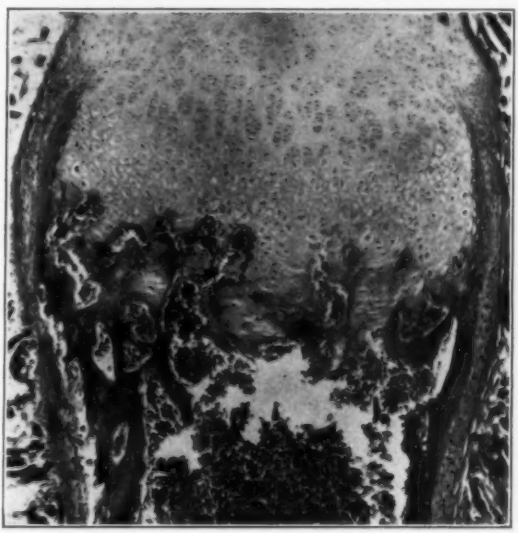

Fig. 3.—Ferric chloride diet; active rickets; section of costochondral junction (×104).

lent in metallic iron content to that of the ferric chloride diet. All the rats in these two groups showed rickets almost as severe as that of the members of the ferric chloride group although the diets were not as well taken and the rats failed to gain weight.

The members of Group 11, fed on a diet containing ferrum reductum, took their diet very poorly and lost weight. In Group 12, which received a diet containing organic iron, the loss of weight was even more pronounced. In these two groups the gross evidences of rickets were lacking. These findings are quite compatible with the well-known requirement of growth for the production of experimental rickets. In fact, it has been shown that cessation of growth resulting from starvation may readily heal the lesions in animals previously rachitic.[3]

The degree of rickets present in the roentgenograms of each group was assessed by Dr. Edward C. Vogt,* without prejudice of previous knowledge of the diets. His reports as shown in Column 7 of Table II stated that severe active rickets was present in the members of Groups 4 and

Fig. 4.—Roentgenograms of lower extremity. Left: Control; no rickets. Right: Ferric chloride diet; advanced active rickets.

7 (Steenbock rachitogenic diet), Group 2 (ferric chloride diet), Group 9 (ferric ammonium citrate diet), and Group 10 (ferrous chloride diet).

CHEMICAL ANALYSES

In Column 6 of Table II are summarized the estimations of serum phosphorus on the pooled blood from each group. The serum phosphorus of all the groups showing no evidence of rickets (Groups 1, 3, 5, 6, 8, 12) varied between 5.6 and 7.8 mg. per cent. That of all the groups showing gross evidence of rickets (Groups 2, 4, 7, 9, 10) was between 3.7 and 2.5 mg. per cent. Group 11 which failed to show gross evidence of rickets showed nevertheless a decrease of the phosphorus to 3.6 mg. per cent.

*We are greatly indebted to Dr. Edward C. Vogt, Roentgenologist to the Infants' and Children's Hospitals, for his assistance in the taking and interpretation of the roentgenograms.

HISTOLOGIC EXAMINATION

The sections of the principal organs showed no evidence of any morbid processes.

Sections of the knee joint, including the lower end of the femur and the upper end of the tibia, and of the costochondral junctions were sub-

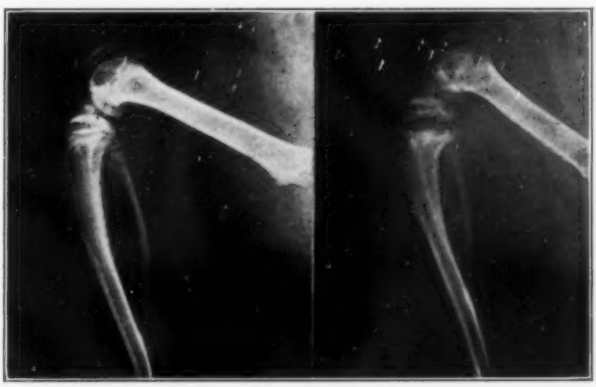

Fig. 5.—Roentgenograms of lower extremity. Left: Control; no rickets. Right: Steenbock diet; advanced active rickets.

Fig. 6.—Roentgenograms of lower extremity. Left: Ferrous chloride diet; advanced active rickets. Right: Iron ammonium citrate diet; advanced active rickets.

mitted to Dr. Sidney Farber* for examination without any indication as to their source. His report, summarized in Column 8 of Table II, corroborates the findings in the roentgenograms. Severe active rickets was present in Groups 4 and 7 (Steenbock rachitogenic diet), Group 2 (ferric chloride diet), Group 9 (ferric ammonium citrate diet), and

*We appreciate the cooperation of Dr. Sidney Farber, Pathologist to the Infants' and Children's Hospitals, in reviewing the pathologic sections.

Group 10 (ferrous chloride diet). In his opinion, the rickets in the members of Group 2 (ferric chloride diet) was more severe than that found in the members of Groups 4 and 7 (Steenbock rachitogenic diet). In Groups 9 and 10 (ferric ammonium citrate diet and ferrous chloride diet), the rickets was slightly less severe. The members of Group 11 (ferrum reductum diet), which had taken their food poorly, had lost weight and had shown no gross manifestations of rickets, nevertheless, presented evidence of having typical rickets, in a moderate degree, by microscopic examination of sections (from the bones of the lower extremities and from the costochondral junctions). There was no microscopic evidence of rickets in Group 12 (organic iron diet) where the loss of body weight had been so great. There was no *qualitative* difference between the rickets produced by these various diets.*

DISCUSSION

A high ratio of Ca to P in the diet has been utilized for a decade in the production of experimental rickets. This principle underlies the Steenbock rachitogenic diet No. 2965 used in Groups 4 and 7. It is believed that the high ratio of calcium to phosphorus in the intestinal tract interferes sufficiently with the absorption and utilization of phosphorus to make this diet rachitogenic.

The knowledge that elements other than calcium when added to the diet may produce rickets is not new. In 1908 Stoeltzner[4] reported that feeding of strontium to animals led to the development of a rachitic process. This has been confirmed several times.

An elaborate investigation by Lehnerdt[5] in 1910 on puppies and young rabbits showed that strontium produced a marked increase in osteoid tissue in the bones, which he called strontium sclerosis. More recently in 1922, Shipley, Park et al.,[6] by adding 2.2 per cent of strontium carbonate to an otherwise normal diet, produced in rats histologic changes of the rachitic type. These abnormalities could not be prevented by the addition of cod liver oil or liberal amounts of viosterol. Many of the rats developed incomplete or total paralyses of the extremities. No relation has ever been demonstrated between strontium and the natural occurrence of infantile rickets.

The close relationship of magnesium to calcium in the production and especially in the healing of rickets has been known for some time. In 1932, Hörste[7] produced in rats rickets of the low phosphorus type by the addition of magnesium carbonate to a nonrachitogenic diet. He showed that the rickets might be regarded as dependent upon the ratio of magnesium plus calcium to phosphorus.

*We are greatly indebted to Dr. S. Burt Wolbach, Professor of Pathology, Harvard Medical School, for allowing us to quote him regarding the rickets produced in these experiments by the ferric chloride diet as histologically typical of low phosphorus rickets, and indistinguishable from that produced by the Steenbock diet.

In 1931, Branion, Guyatt, and Kay[8] reported briefly the production of bone lesions similar to rickets in young rats by the replacement of the calcium carbonate in Steenbock's rachitogenic diet No. 2965 with an equivalent amount of beryllium carbonate. They have expanded these observations more recently (1933) and have shown that the administration of cod liver oil, viosterol, or ultraviolet light in generous amounts does not prevent the onset of this type of rickets.[9] They mention that sections of the bones of their animals show striking differences from the appearances usually encountered in low phosphorus rickets.

Cox, Dodds, et al.,[10] in an excellent, brief report, have shown that the addition of ferric or soluble aluminum salts to the diet of guinea pigs and rabbits interferes with the absorption of phosphorus from the intestinal tract, and claim that this effect is produced by the precipitation of phosphorus in the intestinal tract as ferric and aluminum phosphates.

Waltner, in 1927, published in the German literature evidence that reduced iron added to a nonrachitogenic diet produced rachitic-like changes in rats.

In the investigations described in this paper, it has been established that the addition of large amounts of ferric chloride to a nonrachitogenic diet can render that diet rachitogenic to rats. The chlorine radical of the ferric chloride has been eliminated as the rachitogenic agent by the use of a control diet containing the same weight of chlorine in the form of ammonium chloride. It has been shown that this "ferric chloride rickets" can be prevented by the addition of excess phosphate sufficient theoretically to combine with all the ferric chloride as ferric phosphate. Ferrous chloride and ferric ammonium citrate have been shown to produce the same degree of rickets when added to the control diet in amounts equal in metallic iron content to the ferric chloride used in the ferric chloride diet. Partial evidence has been adduced that reduced iron behaves in the same way.

The rickets produced by the addition to the control diet of the aforementioned amounts of iron was, in these experiments, indistinguishable by roentgenogram, by chemical studies, and by microscopic examination of the tissues from the rickets produced by Steenbock's rachitogenic diet No. 2965.

With these facts established, it is interesting to speculate briefly as to the mechanism of the production of "iron rickets." The experiments were based on the assumption that iron might enter into chemical combination, in the intestinal tract, with phosphorus, to form compounds which are relatively difficult for absorption. There is considerable support in the results for the view that this actually happens.

The serum phosphorus was low in all the members of the rachitic groups. The fact that the ammonium chloride diet gave negative results eliminates the possibility that the addition of ferric chloride produces

rickets by its effect on the hydrogen ion concentration of the intestinal contents. That it is actually the iron radical, which is responsible for the rickets, is shown by the similar effect of the other iron compounds used. The prevention of the rachitogenic effect of the ferric chloride by the addition of extra phosphate in amount sufficient, theoretically, to "hold" all the iron as ferric phosphate is very striking evidence in favor of the simple nonabsorption interpretation.

The data presented in the literature by other investigators suggest a similar simple nonabsorption explanation. The striking figures of Cox, Dodds, et al.[10] supply convincing evidence that ferric salts administered to rabbits and guinea pigs can seriously interfere with the process of absorption of phosphorus. In the experimental rickets induced by the addition to normal diets of beryllium, strontium, and high ratios of calcium and magnesium to phosphorus, it has been suggested that these elements also interfere with the absorption of phosphorus from the intestinal tract. However, this theory has not been satisfactorily proved as yet. And on the evidence so far available, it cannot be claimed that the simple nonabsorption mechanism is the only factor responsible for the production of "iron rickets."

Strontium and beryllium are not in common use as medicinal agents and, therefore, can have no relation to the occurrence of human rickets. Iron, however, especially in the form of the ammonium citrate salt, is now widely used in large doses as a medicinal agent, and the question arises whether it might occasionally be causative of infantile rickets. In considering this possibility it must here be emphasized that the amounts of iron used in these experiments on rats are, in relation to body weight, approximately twenty times the maximum dose of iron usually administered to a child. This fact makes it seem unlikely that the results of these experiments possess clinical significance. Large doses of iron have now been used for many years in both adults and children without raising any clinical suspicions of disturbed phosphorus metabolism. It is conceivable, however, that long continued use of large doses of iron in a child on a diet somewhat low in phosphorus might lead over a prolonged time to the same result as a diet containing a considerable reduction below the optimum in phosphorus. Typical rickets might not appear, but later in life evidence of malnutrition of the bones might develop, as for example, the transverse lines seen occasionally in the roentgenograms of long bones. The relationship of iron therapy to phosphorus and calcium metabolism is being studied by means of human balance experiments and will be reported upon at a later date. Likewise, the possible effect of phosphorus on the absorption of iron and the metabolism of iron in the anemia present in infantile rickets are being investigated.

SUMMARY

1. Rickets has been produced in rats by the addition of ferric chloride to a normal, nonrachitogenic diet.

2. The rickets so produced, as judged by roentgenograms, by microscopic studies, and by chemical studies, was qualitatively similar to, but more severe than that produced by Steenbock's rachitogenic diet No. 2965.

3. The addition of phosphorus to this ferric chloride diet prevented the occurrence of rickets.

4. The chlorine radical of the ferric chloride has been eliminated as the rachitogenic factor by negative results from the addition of ammonium chloride to the nonrachitogenic diet.

5. Similar rachitic changes have been produced by the addition of other iron compounds to the nonrachitogenic diet.

6. The experimental and clinical significance of these findings has been discussed.

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A COMPARISON OF THE NUTRITIONAL AND GROWTH VALUES OF CERTAIN INFANT FOODS

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RECENT interest in infant feeding has been centered principally about the use of unsweetened evaporated milk as an infant food. It was only a few years ago that most of the authorities on infant nutrition looked upon the use of the various varieties of canned milk with askance, and it was not until 1929, when the experimental work of Marriott and Schoenthal[1] was published in regard to the merits of evaporated milk in the feeding of infants, that this prejudice was removed to any considerable extent. Later investigators have raised but few dissenting voices. It is almost unbelievable that medical opinion on such an important matter could be so completely reversed in such a short time, particularly in the absence of any great amount of well-planned and carefully controlled experimental work among infants.

The conviction is still prevalent in the minds of many physicians that fresh cow's milk is the infant food of choice where breast milk is not available. On account of this contention and also because of the stringent need for cheaper infant foods, we have attempted to evaluate the nutritional and growth values of three of the more commonly employed formulas, using breast milk as a control, viz.: (a) certified milk and milk sugar; (b) evaporated milk and milk sugar, and (c) Marriott's[2] lactic acid evaporated milk and Karo mixture.

Ample opportunity for such study of bottle-fed infants was afforded in the Memorial Mercy Home, New Orleans, where a large number of infants are born annually, many of them remaining in the institution throughout the first six or eight months of life. For the breast-fed, or control, group we elected to use the breast-fed infants attending two of the child welfare clinics in New Orleans.

METHOD

Sixty bottle-fed infants and twenty breast-fed infants were observed from birth through the first six months of life, the period of study extending from May, 1931, to January, 1933.

The bottle-fed infants were divided into three groups of twenty infants to a group, and each group was given one of the three formulas

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Financial aid to this experiment was given by the Evaporated Milk Association.

described below throughout the period of observation. These infants were strictly institutional cases, in the Memorial Mercy Home where from fifty to sixty babies were cared for daily through routine methods. No attempt was made at selection, except that those cases were utilized whose expected stay in the institution would extend through the first six months of life. In a few instances cases were rejected on account of congenital defects, which, we felt, might have caused misleading results. The formulas were numbered "1," "2," and "3," and the infants were assigned chronologically in sequence of birth. We thus avoided the inclination to give any infant a particular formula; our aim was to eliminate from the experiment any patient that could not progress satisfactorily on the formula assigned in this way.

The control, or breast-fed group, represents the first twenty infants successfully breast fed over a period of six months while attending two of the child welfare clinics in New Orleans. These infants of the poorer class private home were brought to the clinics every two weeks for supervisional care. The mothers were instructed in the principles of general care on their visits to the clinics and such instruction was augmented by frequent follow-up visits to the homes by trained nurses. It is believed that in this way instructions were carried out completely in the majority of instances.

In the beginning we attempted to feed the lactic acid evaporated milk and Karo formula as suggested by Marriott, but on account of vomiting and diarrhea among the infants one or two months of age, we were forced to abandon it. We found that by diluting this formula one-third by volume with sterile water such difficulties were obviated. Such dilution gives a mixture which represents approximately 20 calories per ounce, 8.7 per cent carbohydrate, 2 per cent protein, and 2.7 per cent fat. In order to harmonize the food concentration in the three different formulas and to maintain as nearly as possible in all three mixtures similar ratios between the carbohydrate, protein, and fat, the other two formulas were contructed so as to conform in these respects quite closely with the diluted lactic acid evaporated milk and Karo formula described above.

The bottle-fed infants were fed on the assumption that the age in months plus two equals approximately the stomach capacity of the child. The majority consumed less than this amount of food every three hours, six feedings daily. Most of the infants made satisfactory progress on 45 calories per pound of body weight in 24 hours while a few of them required from 50 to 55 calories. No increase in the concentration of the formulas was made with the increase of age, but formulas of the same strength were used throughout the experiment. As long as the weekly gain in weight was satisfactory for the age of the child, no increase in the food intake was made.

TABLE I

SYNOPSIS OF COMPOSITION AND PREPARATION OF FORMULAS

Formula No. 1.		
Certified milk, boiled for 3 minutes	500.00 c.c.	Equals approximately 19 calories per ounce, 8.5 per cent carbohydrate, 1.7 per cent protein, and 2 per cent fat.
Milk sugar	70.00 gm.	
Lime water	60.00 c.c.	
Boiled water, enough to make	1,000.00 c.c.	
Formula No. 2.		
Evaporated milk	250 c.c.	Equals approximately 19 calories per ounce, 8.5 per cent carbohydrate, 1.7 per cent protein, and 2 per cent fat.
Milk sugar	70.00 gm.	
Boiled water, enough to make	1,000.00 c.c.	
Formula No. 3.		
Corn syrup	90.00 gm.	
Lactic Acid (U.S.P.)	5.00 c.c.	
Boiled water, enough to make	500.00 c.c.	

The above acid sugar solution was added to 500.00 c.c. of evaporated milk and the resulting mixture diluted with 333.00 c.c. sterile water. This equals approximately 20 calories per ounce, 8.7 per cent carbohydrate, 2 per cent protein, and 2.7 per cent fat.

All infants were given sun baths outdoors routinely when the weather permitted. It should be stated in this connection, however, that this phase of the general care of the bottle-fed infants was inadequate because the necessary facilities were not available, except on warm days when the cribs could be taken outside on open porches. This attention to the breast-fed, or control, group was carried out more fully, since these infants were in private homes where individual attention was possible.

Both breast- and bottle-fed infants received a standard brand of 10-D cod liver oil in the following amounts: from the second week to the first month 20 minims, three times a day; from the first to the third month 40 minims, three times a day; and from the third to the sixth month 60 minims, three times a day. Also orange juice was given to all infants as follows: from the second week to the first month 15 minims, twice a day; from the first to the second month 30 minims, twice a day; from the second to the third month 60 minims, twice a day; and from the third to the sixth month one-half ounce, twice a day. Cereal gruel was added to the diets at five months, and strained vegetable broth and cooked cereal were added at the sixth month.

Clinical records, kept on each case separately, included bimonthly physical examinations, semiweekly weight records on the bottle-fed infants and biweekly weight records on the breast-fed infants, nutritional defects with particular reference to rickets, the number and kind of infections, the presence or absence of gastrointestinal upsets, the state of nutrition, general condition, and physical attainments of each child.

At the end of the third and at the end of the sixth month of life, roentgenograms were made of the bones of both upper and lower extremities of all infants. The calcium and inorganic phosphorus content of the

blood serum was determined at the end of the third month and, in most cases, at the end of the sixth month in the bottle-fed infants. The breast-fed infants were excluded from the serologic determinations, because of objection on the part of parents to sinus puncture. The blood was collected by puncture of the longitudinal sinus, and the determinations were made shortly afterward. The method employed for the determination of calcium was that described by Clark and Collip[3] while the inorganic phosphorus was determined by the method of Fiske and Subbarow.[4]

Clinical rickets was diagnosed mainly on the basis of three signs, viz: (a) enlargement of the epiphyses; (b) beading of the ribs at the costo-

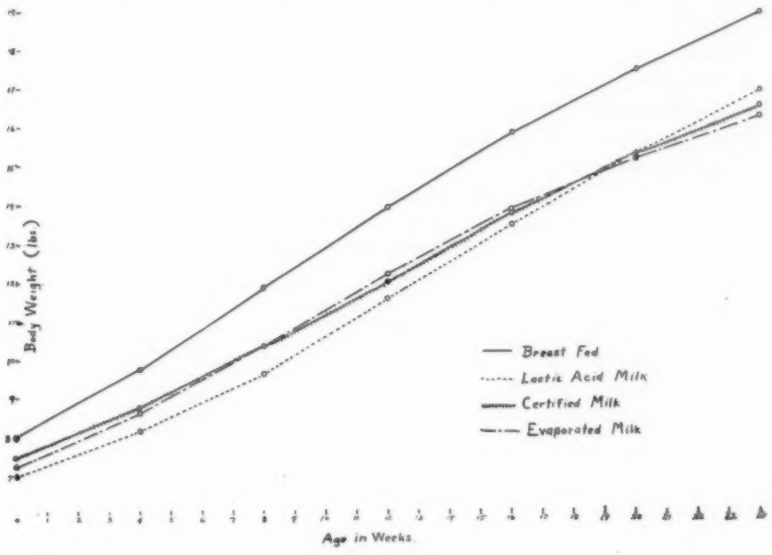

Chart 1.

chondral junctions, and (c) anemia and flabbiness of muscles. Other signs, such as head sweating, constipation, abdominal enlargement, and cranial bosses, were taken into account and recorded. The radiologists (Drs. E. C. Samuel and E. R. Bowie) reported their findings in the case of rickets as "negative," "mild," "moderate," or "severe," depending upon the degree of bone changes noted.

Weight curves have been plotted to show the average birth weight of each group, as well as the average monthly gain in weight for each group. Table I gives a synopsis of the preparation and composition of the three formulas employed, and Table II shows the average birth length and birth weight of each group and the average monthly gain in length and weight during the period of study.

RESULTS

Referring to the weight curves, it will be noted that the control, or breast-fed group of infants, made a much more rapid gain in weight than did any of the bottle-fed groups although the bottle-fed infants exceeded the normal expected gain in weight by the sixth month. Further it will be noted that the progress in growth of the breast-fed infants was more uniform and was not broken by the number of interruptions that were present among the bottle-fed infants.

The breast-fed infants were more vigorous, showed better tissue turgor, better osseous and muscular development, and were strikingly superior to the bottle-fed infants in physical attainments, such as the time of holding the head erect, the time of sitting up and the time of teething. By consulting Table II, which gives the average length and weight of the breast- and bottle-fed infants from birth to the sixth month, it will be noted that the average length of the bottle-fed infants nearly equals that of the breast-fed infants while the average weight of the breast-fed infants exceeds that of the bottle-fed infants by almost three pounds at the sixth month.

TABLE II

AVERAGE LENGTH AND WEIGHT OF INFANTS FROM BIRTH THROUGH THE SIXTH MONTH

BREAST-FED GROUP—20 INFANTS		
AGE	LENGTH	WEIGHT
Birth	20.0 inches	8.0 pounds
1 month	21.9 inches	9.7 pounds
2 months	23.6 inches	11.8 pounds
3 months	25.0 inches	13.9 pounds
4 months	26.5 inches	15.8 pounds
5 months	27.4 inches	17.5 pounds
6 months	28.0 inches	18.9 pounds
BOTTLE-FED GROUPS—60 INFANTS		
AGE	LENGTH	WEIGHT
Birth	19.8 inches	7.25 pounds
1 month	21.7 inches	8.4 pounds
2 months	23.3 inches	10.5 pounds
3 months	24.7 inches	11.9 pounds
4 months	26.1 inches	13.7 pounds
5 months	26.7 inches	15.2 pounds
6 months	27.7 inches	16.5 pounds

At almost any time during the period of study, as many as one or two infants could be found in any one of the bottle-fed groups, who for one reason or another were not making satisfactory progress, but on the whole, the nutrition and growth of these infants remained quite good. Diligent attention to diet was necessary in order to maintain uniform progress among the bottle-fed infants, and this was particularly true of the group fed on boiled certified milk and milk sugar, primarily because of indigestion and constipation among the members of this group.

The three different formulas employed gave so nearly the same results in growth and nutrition that it is not considered worth while to attempt any contrast of the slight differences, and we shall consider it sufficient simply to call attention to the weight curves of the bottle-fed infants and to state that as a whole, the group fed on the dilute lactic acid evaporated milk and Karo formula excelled the other two bottle-fed groups somewhat in quality of nutrition.

Clinical diagnosis of rickets was made in 35 per cent of the breast-fed infants and in 85 per cent of the bottle-fed infants, the radiologists reporting the disease in 90 per cent of the bottle-fed infants and in 35 per cent of the breast-fed infants. There was no difference in the incidence of rickets among the infants receiving the three different formulas. Severe rickets was present in only a few cases of the bottle-fed infants; the breast-fed infants and the vast majority of the bottle-fed infants presenting the condition in mild or moderate form. There was no case of scurvy or tetany observed or any obvious evidence of lack of the accessory food factors in the diets.

The average calcium level of the blood serum of the three bottle-fed groups was 10.41 mgm. per cent at the third month and 10.36 mgm. per cent at the sixth month, while the average level of the inorganic phosphorus of the blood of these infants was 5.65 mgm. per cent at the third month and 4.87 mgm. per cent at the sixth month. It will be seen from these figures that the average calcium-phosphorus product was 51.81 (10.41×5.65) at the third month and 50.45 (10.36×4.87) at the sixth month, notwithstanding the facts that 85 per cent of these infants had rickets according to clinical evidence and that the radiologists reported the disease in 90 per cent of the bottle-fed series.

The usual types of infection were encountered in both the breast and bottle-fed groups, such as the acute upper respiratory infections, acute bronchitis, tonsillitis, acute otitis media, impetigo, pyelitis, pneumonia, and generalized furunculosis. Particularly acute otitis media, impetigo, and generalized furunculosis were more prevalent among the bottle-fed members, but there did not seem to be any difference in susceptibility to infection among the infants of the different bottle-fed groups.

Although nearly all of the breast-fed infants had frequent attacks of colic during the first two or three months of life, such disturbance rarely retarded the progress of the child. These attacks were characterized by marked fretfulness, abdominal distention, and greenish colored stools that were strongly acid in reaction and contained large amounts of mucus and curds. There was considerable rumination shortly after feedings, at times actual vomiting, and in a few instances such attacks terminated in fermentative diarrhea. After the third month the breast-fed infants rarely showed any digestive disturbance, except in the occasional case, where over-feeding was usually at fault. Constipation was seldom met with among the breast-fed infants, their stools being of bright

yellow color, of almost liquid consistency, of a slightly sour odor, and acid in reaction. Except in cases of indigestion, or colic, the stools were smooth and contained no mucus or curds.

The group of infants fed on boiled certified milk and milk sugar had frequent gastrointestinal upsets, with symptoms that often called for temporary change of diet. These upsets were more frequent during the early months of life, but they also recurred quite often throughout the period of observation, definitely placing this group of infants first in rank in the number of feeding difficulties encountered among the bottle-fed groups. Stubborn constipation was quite prevalent among these infants and was apparently the forerunner of many of their gastrointestinal upsets. We were forced to administer milk of magnesia almost daily in order to overcome the constipation. These infants did not handle the boiled certified milk with the same ease of digestion that was apparent among the other two groups fed on the evaporated milk formulas. Their stools were of light yellow color, from semisolid to firm in consistency, alkaline in reaction, and often contained large curds, mucus, and other evidence of undigested food. In three instances patients were dropped from the experiment on account of their inability to handle the formula assigned them, two of them having had boiled certified milk and milk sugar and the other evaporated milk and milk sugar.

The group of infants fed on evaporated milk and milk sugar showed better digestion and, consequently, fewer gastrointestinal upsets than did the group fed on boiled certified milk and milk sugar. There was, however, an appreciable difference in the facility with which this formula was handled as compared to the dilute lactic acid evaporated milk and Karo formula, the latter being much more readily digested. The stools of this group of infants were of light yellow color, semisolid in consistency, alkaline in reaction, and did not often show evidence of undigested food.

The group of infants fed on the dilute lactic acid evaporated milk and Karo formula rarely showed any signs of indigestion and had fewer gastrointestinal upsets than any group of infants observed. They were easily managed from the standpoint of diet, their appetites being consistently better than for either of the other two bottle-fed groups. The tendency toward constipation was much less marked in this group of infants, their stools being of smooth pastelike consistency, grayish in color, and alkaline in reaction.

COMMENT

It would probably be unfair to assume that there is normally as great a difference in the growth and development between breast-fed infants and bottle-fed infants as our results would indicate. The parents of the control, or breast-fed group, were nearly all of Italian or Irish extrac-

tion, of the large, robust type individual, many of the mothers having had five or more children previously, who had been successfully breast fed. After checking the diets of these mothers, it was found that most of them ate heartily and that their diets contained liberal amounts of fresh vegetables, fruits, milk, meat, and eggs. They were hard-working women, engaged in household duties, who had little time in which to develop the neurotic chain of symptoms that often interfere with breast feeding. It was not our purpose to select this particular type of mother, but she seemed to be the predominating type among those coming to the clinics who could successfully nurse their infants without the aid of complemental or supplemental feedings. Then again, we have individual care in the private home in the case of the breast-fed infants as against institutional environment and institutional care in the case of the bottle-fed infants. The supply of breast milk in the majority of instances was plentiful, many of the mothers having sufficient amount to have nursed two healthy infants. We believe that the sum total of these factors would bring the control, or breast-fed group of this experiment, well beyond what is ordinarily considered good conditions for breast feeding.

Considering the results we have obtained in growth and nutrition by use of the three formulas, it would be logical to presume that it makes little difference what milk is used, so long as the diet is balanced in the essential food constituents, is adequate in amount, is within the digestive capacity of the child, and contains the necessary vitamins. There is no doubt that evaporated milk is more easily digested than fresh cow's milk, regardless of upon what the crux of the explanation of this fact may depend. The ease with which a food is digested and the presence or absence of the aggravating symptoms of indigestion are important matters in the feeding of infants. It was due to these difficulties that we found the group of infants fed on the boiled certified milk and milk sugar so troublesome to feed. Feeding difficulties are not always reflected in the end-results obtained in nutrition and growth; our control group of breast-fed infants nearly all had digestive difficulties during the first two or three months of life, as well as the group fed on boiled certified milk and milk sugar, and both of these groups made good progress in nutrition and growth at all times during the period of observation.

It appears in this experiment from the parallel feeding of the different groups of infants on fresh cow's milk and evaporated milk formulas, that the difference in the digestibility of these two forms of milk depends largely upon the difference in curd tension. The changed state of the milk protein brought about by the superheating of evaporated milk, as well as its homogeneity, are perhaps characters of decided importance. Rice[5] demonstrated the soft curd of evaporated milk, and later Brennemann[6] emphasized its practical application to infant feeding. The work of Willard and Blunt[7] on the retention of calcium, phosphorus, and nitrogen, by infants fed on pasteurized milk and on evaporated milk,

would seem to indicate that more of these elements are retained in the blood when evaporated milk is used. Our results do not substantiate these findings, so far as the retention of calcium and phosphorus are concerned.

We are not convinced that young infants may be fed whole milk to good advantage, whether acidified or not. One of us (Williams) has endeavored on other occasions to feed young infants the lactic acid evaporated milk and Karo formula suggested by Marriott, but has consistently met with the same results, vomiting and diarrhea. It had been thought that these difficulties might be due in part to the warm climate in this section of country, but we note that other writers north of us[8] have recently reported similar findings. We concur in the almost unanimous opinion that the addition of lactic acid to milk renders it more digestible and increases the safety level to which carbohydrate may be added to the formula, but it is obvious that the degree of this improvement is yet undetermined, as evidenced by our inability to feed the concentrated whole milk mixtures to young infants. We consider the lactic acid evaporated milk and Karo formula more or less ideal for the routine feeding of infants, provided the concentration is kept within the digestive limits of the child to be fed. It is particularly well adapted to the feeding of institutional infants, due to the fact that it is readily prepared, easily fed, and is utilized well by the vast majority of infants. In fact, our results have been so uniformly satisfactory from the use of this formula that it has been adopted as the standard feeding mixture in the Memorial Mercy Home, but modified for the first three months of life as described under "Method." After the first three months, we now feed the whole lactic acid evaporated milk and Karo formula as suggested by Marriott.

As a result of past experience in attempting to feed whole lactic acid milk to young infants and of former teachings with reference to the use of canned milk in general, this experiment was begun with considerable prejudice against the routine feeding of lactic acid milk and with certain reservations that were derogatory to the use of evaporated milk. This study was instituted primarily to settle these questions in our own minds so that we might proceed with greater assurance and with prejudice or doubt dispelled. At the conclusion of this work, after feeding groups of infants of the same age and under the same environment on fresh cow's milk and on evaporated milk with almost identical results in nutrition and growth, our attitude has naturally been materially changed. We no longer frown on the use of evaporated milk as an infant food, but we believe that it is just as good as certified milk, with these added points in its favor: it is more easily digested, consequently, causes fewer gastrointestinal disorders; there is less danger in its use where refrigeration is in question; it is produced under national government regulations, which circumvents petty politics so often met with in various cities prohibiting

the passage of the proper milk ordinances; it facilitates the preparation of formulas and is much cheaper.

Considering the number of infants of this study who had rickets, it would seem that the incidence of the disease is unusually high, although DeBuys and von Meysenbug[9] reported 34 per cent of breast-fed infants as having rickets in this locality in 1924. Attention should be called to the close check between the clinical and roentgenologic evidence in arriving at a diagnosis of rickets among these infants and to the comparatively worthless application of the calcium-phosphorus product criterion. Either the standard of 40 as the normal product is low, or else these elements exist in the blood of rachitic infants in a changed state from that of the normal infant. The average calcium and phosphorus products were well above 40, both at the third and at the sixth months of life, yet 85 per cent of the infants under observation showed rickets.

SUMMARY

Sixty infants were divided into three groups of twenty, and each group was fed one of three different formulas from birth through the sixth month, the results obtained in nutrition and growth being compared to corresponding results obtained by feeding twenty infants on breast milk over a similar period of time.

Each individual was closely checked for quality of nutrition, growth and development, nutritional diseases, digestive disorders, and for the number and types of infection.

At the end of the third and of the sixth months of life, roentgenograms were made of the bones of the upper and lower extremities on all cases, and at these same intervals the serum calcium and inorganic phosphorus were determined on the bottle-fed infants.

Curves have been plotted to show the average birth weight, as well as the average monthly gain in weight of each group from birth through the sixth month. Table I gives a synopsis of the preparation and composition of the formulas used while Table II shows the average birth length and birth weight of the various groups and the average monthly gain in these factors from birth to the end of the sixth month.

Effort has been made to compare the results obtained by feeding the three different types of formulas and to give some reasons for the conclusions as to which is best adapted to the general routine feeding of infants.

CONCLUSIONS

The results in nutrition and growth obtained by feeding fresh cow's milk and evaporated milk formulas were almost identical. Evaporated milk being more easily digested than fresh cow's milk, caused fewer gastrointestinal upsets and was less difficult to feed.

The addition of lactic acid to milk renders it more digestible and increases the safety level to which sugar may be added to the formula. The lactic acid evaporated milk and Karo formula suggested by Marriott was poorly tolerated by infants under three months of age, but when diluted one-third by volume with sterile water, these difficulties were obviated. This formula was more easily digested and was easier to feed than either the fresh cow's milk formula or the evaporated milk formula; it gave excellent results in growth and nutrition and is recommended for the general routine feeding of infants less than three months of age.

The incidence of rickets among the infants of this study was high, particularly so, since all of them received rather large amounts of cod liver oil routinely, as well as sunshine outdoors. There was no difference in the incidence of rickets or in the frequency of infections among the members of the different bottle-fed groups.

The clinical and x-ray findings in the case of rickets checked quite closely while the serologic evidence was entirely out of line with the usual accepted standards.

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ON THE MOTION OF GROWTH

XVI. Clinical Aspects of Human Growth and Metabolism With Special Reference to Infancy and Preschool Life

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INTRODUCTION

CLINICAL interest in human growth is centered upon three principal phases of the problem. The first is clearly concerned with the events of growth itself as these are displayed by data, collected in the mass or from observations upon individual subjects, which define the age trend of changing size in presumably healthy infants or children. The second relates to the highly important matters of nutrition, but more specifically to the success or to the failure of various nutritive substances in promoting and in supporting the processes of growth. The third phase, equally distinctive in its primary objects, though it is unmistakably linked with each of the former, deals with the phenomena of energy exchange as judged especially by the production and liberation of heat.

Taken together these three phases are intimately related to the general problem of income, balance, and outgo of energy. Each has been thoroughly and widely examined in the laboratory, as well as in the clinic, and the chief results have found extensive application in the routine care of infants and children. But in the absence of some single unifying principle, much of this information has been treated as discrete or, when considered to be related, it has been treated only vaguely so. A fresh outlook, however, upon the many collateral problems in these three fields, as well as a clearer understanding of them ought now to be assured by the dynamic connection which we have been able to establish between the events of pure growth on the one hand and those of heat production or "metabolism" on the other.[1] Certain introductory features pertaining to the clinical side of the subject have already been described.[2] Among other things we have placed special emphasis upon such basic matters as the definition of growth, the careful distinction between true growth and ordinary gain, the broad underlying scheme of energy exchange, and the differentiation between basal heat output and maintenance rate of heat production.

With these results in mind we shall now work forward to a discussion of various problems of growth and metabolism which possess noteworthy clinical importance, restricting our selection of these to such as arise

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during infancy and preschool life. We shall prepare, in particular, to consider one of the handicaps to growth which makes the rearing of premature infants a difficult task; the accidental character of the loss in weight at birth; the rate of gain during infancy, and finally, in describing the metabolism of the preschool child, to offer a new interpretation as to the physiologic background of anorexia so frequent at this stage of life. Similar problems of adolescence such as "spurts of growth" and "spurts of metabolism" will be deferred to a later time.

To accomplish these purposes it will be necessary to investigate quite intimately the life trends of both growth and basal heat production throughout the entire span of infancy and childhood. The first step in this direction is to establish the units in which each of the latter is most suitably measured.

Preliminary Survey of Items Essential to the Study of Growth and Metabolism

To begin with, we shall find it useful, as previously indicated, to consider the matters of growth hand in hand with those of heat production or "metabolism." In fact, a complete analysis of growth requires such treatment, for the nature of this process cannot be properly understood by detailing merely successive changes in size. The traditional method of portraying and of studying "growth" almost exclusively in terms of items (1) and (2) in Table I suffices, it is true, for some clinical purposes. But it is necessary, if satisfactory information on the subject is desired, to deal with each of the other equally important items in this table. For this reason, though even more because of the extreme importance of distinguishing clearly between "cumulative gain" (item 1) and "true growth" (item 4), and hence, between rate of gain (item 2) and rate of growth (item 5), we shall enlarge upon the characteristic differences which are but briefly presented here. Special attention will therefore be directed to the life trends of these four components in addition to the corresponding trends exhibited by items (7) and (8). The latter, as we have elsewhere shown,[1] are not only intimately related to, but are actually dependent upon several of the functions listed under "growth," the chief of which is item (5) and its square.

LIFE TRENDS OF GROWTH AND METABOLISM

Curves of Weight and Rate of Gain (Fig. 1, z and z')

Because of its familiarity we shall speak of "growth" primarily in terms of weight, and shall consider at the outset the cumulative changes in weight that are, on the whole, characteristic of healthy subjects over the entire, or almost entire life cycle. The description is best followed by keeping in mind and by comparing the simultaneous changes in both

weight and rate of gain throughout the entire epoch of "growth" as given by the respective curves z and z' in Fig. 1, which embody the results of an analysis originally reported as our Series XIX.[1] The prenatal phase, too minute on this chart to be of use on account of scale, is drawn in

TABLE I

A LIST OF ITEMS ESSENTIAL TO THE STUDY OF GROWTH AND METABOLISM AND THEIR CORRESPONDING PRACTICAL UNITS OF MEASURE*

ITEM FOR STUDY	SYMBOL	PRACTICAL UNIT	
"Growth":			
1. Cumulative Increments of Size†	z	Gm.‡;	Kg.
2. §Rate of Change in Size (Rate of Gain)‖	z'	Gm./Day;	Kg./Year
3. Acceleration of Gain	z''	Gm./Day/Day;	Kg./Year/Year
4. Cumulative Increments of Growth (Change in Size per Unit Size—*True Growth*)	q	Gm./Kg.;	Kg./Kg.
5. §Rate of Growth‖	q'	Gm./Kg./Day;	Kg./Kg./Year
6. Acceleration of Growth	q''	Gm./Kg./Day/Day;	Kg./Kg./Year/Year
"Metabolism" (Basal State):			
7. Quantity of Heat Produced per Day	(Uz)	Cal.¶/Day	
8. Quantity of Heat Produced per Unit of Size (Weight) per Day (*True Basal Metabolism*)	U	Cal./Kg./Day	

*A more complete description of the above as well as of other quantities important to growth and metabolism has been given in a recent paper.[3] Of special significance are the fundamental properties of growth described as resistance ρ, inductance λ, and permittance κ, which enter into the scheme of energy distribution and thereby act in conjunction with the above items to assist in defining the successive changes of state throughout growth.[1, 3]

†These, when plotted, form what is customarily, though incorrectly, referred to as "the growth curve."

‡This and the succeeding quantities employing the gm. as the unit of mass are chiefly used for measurements of weight during infancy, the day, as the unit of time, being likewise customary during the same period.

§The square of items (2) and (5), that is (rate of gain)^2 and (rate of growth)^2 respectively, in addition to various products of the above components of growth, also require to be enumerated here.

‖The term "relative rate of growth" has been habitually used as synonymous with "relative rate of gain." But it will be evident that the former of these can have no real meaning as long as we accept the present definition of growth to be, broadly, "a change in size per unit size," wherein the "relativity" of growth is already provided for and explicitly stated. There are several ways in which the foregoing important distinctions may be further clarified. Assume, for example, that the term "relative rate of growth," just now under suspicion, is provisionally equivalent to what is actually represented by the "relative rate of gain" and is measured in Kg./Kg./Day. This would mean, obviously, that "growth" and "gain" are synonymous; as, indeed, they have been considered to be in times past. Such a result, however, is clearly in conflict with the definition that growth is "change in size per unit size," which we have found indispensable to a dynamic study of the problem.[1, 3] The distinctions, moreover, which have heretofore been necessarily made by means of the terms "relative" and "absolute" in connection with rate of change, are now automatically contained in the terms "growth" and "gain" respectively; whence, on the present basis, the expression "relative rate of growth" is precisely equivalent by substitution to "relative-relative rate of gain." From this it is at once obvious that the former, (i.e. "relative rate of growth") can have no significant meaning. There will, accordingly, be no need of distinguishing between "relative" and "absolute" growth or gain, for growth and gain are both "absolute" entities as here conceived and defined. From what has just been said, the connection between growth and gain is best expressed and remembered in the form: Rate of Growth = Relative Rate of Gain (or Loss), either of which is therefore synonymous with "Rate of Reduplication" provided the latter is understood and permitted to assume both fractional and integral values.

¶The large or Kg. calorie.

semilogarithmic fashion to a greatly enlarged scale in Fig. 2, the resulting curve thus automatically displaying the corresponding trend of item (4) and requiring a change of symbol from z to q.* These curves together portray the trend of weight from the one-hundredth day of gestation in fetal life to the thirty-second year of postnatal existence.

The chief characteristics of "growth in weight" are thus seen to group themselves about the two major deflections in the curve describing the rate of gain, z'. The former holds sway over the circumnatal epoch† which includes the late fetal, or premature, natal, and infantile periods

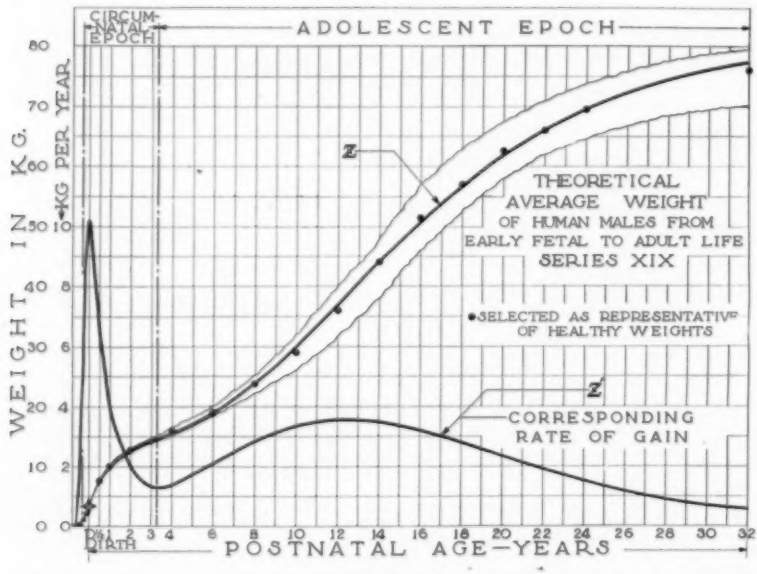

Fig. 1.—Theoretical curves of weight (z) and rate of gain (z') from early fetal to adult life. The boundaries of the white field through which z passes mark what may be considered the ordinary upper and lower limits of weight in healthy children as expressed in the data of a large group of investigators.[7-28]

•It is worth noting here, especially in connection with the discussion regarding the important distinction between *growth* and *gain*, that curves drawn on semilogarithmic grids, such as that for the fetal epoch in Fig. 2, actually display the trend of "true growth" and are therefore properly growth or "q" curves (Table I), whereas those drawn on ordinary arithmetic grids, such as z in Fig. 1, represent simply the trend of cumulative increments in size. (See footnotes to Table I for additional comment on this point).

A more serious error, however, arises when figure legends to curves for cumulative weight, z (item 1, Table I), are made rather frequently to read "showing the rate of growth." It is true, of course, that the changing slope of such curves as, for example, z in Fig. 1, is a measure of the rate of change in size (rate of gain) and that we may infer the result by noting the variations in slope from point to point; but they do not themselves represent the rate of change because this can be directly exhibited only by some corresponding curve such as z' (item 2) in the same figure. By the definitions in Table I it is clear, moreover, that neither z nor z' is, properly speaking, a "growth curve"; for, according to item (4), the specific features in the trend of true growth cannot be graphically presented except by drawing z on semilogarithmic paper, or what is actually the same thing by plotting logarithms of the weight on an ordinary cross-section grid. The rate of growth q' is then given by the corresponding velocity curve of the latter, just as illustrated in Fig. 3.

†Davenport[1] has also employed the terms "circumnatal" and "adolescent," though in connection with, and as referring to, "cycles"; the former beginning at fertilization and ending between two and three years postnatal age, the latter, however, not setting

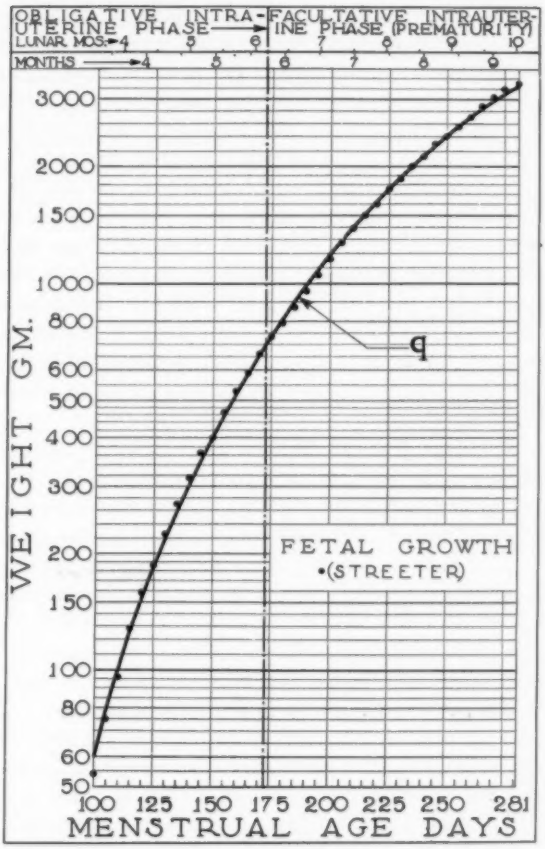

Fig. 2.—The curve for fetal growth from the one hundredth day of menstrual age to birth. The solid circles represent the mean values of every fifth day in the original data of Streeter.[25] The line of demarcation is made, somewhat arbitrarily, to pass through the value 700 gm., the intersection thus occurring at the 173rd day menstrual time.

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in until ten years and lasting until the twentieth year. From the clinical point of view it seems better, however, to date the onset of the circumnatal "epoch" at the time when the possibility of extrauterine existence is first assured. This is, approximately, at the point where the fetus has reached about 700 gm. and hence at about the 173rd day of gestation by menstrual time. Smaller "prematures" have been born and have even thrived (600 gm.),[5] though it is not to be expected that all could necessarily do so much before they had reached considerably greater weights. Neglecting for the moment this difference in the location of boundaries, it may be noted that we prefer to avoid the term "cycle," introduced by Robertson[6] and used since by writers on growth to designate an interval during which the rate of gain rises from, and returns to, its previous low level, because such a period, properly speaking, represents only a half cycle. If, nevertheless, we wished to abide by this custom, and desired, in addition, to place the outer boundary of the circumnatal "cycle" at 3.30 years (as we do) where z' has its minimum value, 1.27 Kg. per year, it would be necessary to move the anterior boundary from the 173rd to the 103rd day of gestation where the value of z' is also 1.27 Kg. per year. Here, however, the fetus weighs but 60 gm. and has no physiologic chance of becoming a natal candidate. Returning once more to the matter of cycles, it may be remarked that the latter notation is primarily avoided in our own work because the curves for weight z and rate of gain z' in Fig. 1 are represented by compound exponential equations such that z and z' can only have the single imaginary period, $2i\pi$, where $i = \sqrt{-1}$.

of life. Its peak is uncannily placed at the moment of normal birth itself, and this is followed by a swift decline throughout the first two years of life, when teeth are erupting, when the blood is changing, and when walking and talking are added to the accomplishments of the "little man." A period of comparative rest follows the impetuous epoch just passed through, as though to prepare for the longer, though less strenuous, period of adolescence ahead, which reaches its own peak, so far as the rate of change in weight is concerned, between the twelfth and thirteenth years. Thenceforth, "growth" (as judged by rate of gain) passes at last into the final stage of gentle decline, to come ultimately to rest when weight has reached its upper stationary value in adult life. These features are widely known; they are not new; but from them we shall try, in the light of results elsewhere reported, to reinterpret the events of "normal growth" as these relate to the care of healthy infants and children.

The trend of weight just described in connection with curve *z* of Fig. 1 corresponds closely to that represented in the majority of data collected by a host of investigators.[7-28] This particular curve is, accordingly, much more similar to the curves derived on the basis of mass statistics than to those plotted from the successive weights of single subjects. The latter are disposed, as we must always expect, to be less regular than the former, and they show frequently what are of late referred to as "spurts of growth." These will receive attention when we come to discuss the clinical aspects of growth during the adolescent epoch, though it is well to point out here, that such spurts under normal conditions, are rarely if ever as prominent during the circumnatal period as they are at later stages of life. But, even though it must be frankly admitted that no child's weight will proceed strictly along the entire course of the curve here described, it may nevertheless be said that the weights of a healthy subject of European or American stock will almost invariably be found scattered somewhere within the field of Fig. 1, which surrounds curve *z* itself. It is correspondingly unlikely that the weight of a healthy child will lie significantly beyond this range, though the weights of special groups, such as the California gifted of Baldwin,[8] and the private school children of Gray and Ayres,[17] will obviously tend toward the upper limit of this field, and even, as in the latter example just referred to, slightly but definitely beyond this boundary.

The trend of the field itself possesses the selfsame characteristics as the curve traversing it. This is not at all surprising since the data, from whatever source, have all been obtained from studies on "more or less" healthy human subjects. For certain purposes it is best to work with a "field" of growth such as that sketched out, any point included therein being justly considered, so far as our observations go, within the range of the healthy, or so-called "normal average" weight at various ages. But, for other purposes, it is equally necessary to fix upon some single

curve passing through this infinitude of points, which then may be held to represent the normal trend in question. We have here deliberately chosen curve *z* of Fig. 1 in part, but only in part, because it represents effectively the general shape, level, and direction which the better data on the healthiest children quite clearly disclose. This particular curve has also been chosen to represent the trend of weight because it has been found, upon further analysis,[1] to possess the very components (especially items 1, 2, and 5 of Table I) which permit its transformation, upon the basis of the scheme of energy exchange previously described,[2] directly into the corresponding curves, for heat production shown in Fig. 4. The former thus constitutes the "growth counterpart" of heat production, and the latter, in turn, the "heat" counterpart of growth. Such a result speaks greatly in favor of the opinion that the weight curve of Fig. 1 is not far removed from what can be considered a legitimate physiologic "norm" of human growth. It provides, likewise, direct evidence that "growth" and "metabolism" are dynamically part and parcel of the same fundamental biologic process. From the theoretical point of view in particular, but also to a great extent, even from the practical side, we are thus justified in placing decided confidence upon this, or for that matter, upon any other weight curve within the field, which, by means of its appropriate components, redescribes the full course of basal heat production. For such a curve is doubly anchored: it is "held" on the one side by the original data on weight, and on the other, by observations of a different kind which have even been made independently of weight itself.

Thus, so far as the clinical importance of weight alone is concerned, curve *z* in Fig. 1 may be taken to represent with some considerable certainty the life trend of this particular unit of human size. No pediatrician will expect that all of his healthy subjects, or even a single one of them will follow the curve exactly, though he will also realize that no healthy child will deviate greatly from it. The failure of a child to pursue this particular trend of increase in weight will not prevent us, on the theoretical side, from conceiving such progress to be possible under an ideal set of conditions. The point just now in question is no doubt of greater analytical than clinical concern, though it seems of sufficient current importance to be noted here, and to be summed up as follows: The weights of healthy children will in general be somewhat above or below curve *z* of Fig. 1, but they will also be distinctly in the neighborhood of this or of some other standard and the latter will likewise lie somewhere within, certainly not far beyond the bounds sketched out.

Curves of Growth and Rate of Growth (Fig. 3, q and q')

Thus far we have viewed the problem of human "growth" in terms of cumulative increments in weight and in terms of the rate of gain. But,

in accordance with the definitions of Table I, neither of these trends can be said to represent the course of true growth correctly. In order, therefore, to distinguish clearly between ordinary gain and growth, as well as between their rates of change, we have brought all four curves together in Fig. 3 with the hope of obtaining the sharpest possible contrasts.* The events and characteristics of true growth, q, and q' in the lower section may thus be simultaneously compared with those of z and z' placed above them. These comparisons are made with reference to weight and rate of gain partly because the latter are bound to be by far the more familiar, and partly too, because we habitually measure "growth" only in terms of simple change in size, and most conveniently in terms of weight itself. We do not, nor can we, measure growth q, directly. Arithmetical approximations to this are even likely to be very seriously in error and more accurate estimations require mathematical analysis too burdensome for ordinary clinical work. The latter remarks apply with still more force to the determination of the rate of growth.

Growth q Compared With Cumulative Weight z.—Aside from easily recognized differences in the general contours of these two curves, the most perceptible difference is perhaps to be found in their relative levels at corresponding points of time. We cannot escape the definite impression that growth q, so far as nearing completion is concerned, keeps well in advance of weight z. This particular effect is most conspicuous during infancy and early childhood although it is likewise noticeable, even if in lesser degree, at later stages of life. Thus we find by actual computation that the quantity of growth q at birth has already reached approximately 25 per cent of its final value, whereas weight z lags far behind in having reached but 4 per cent of its own adult level. Comparing the same items at the end of the circumnatal epoch (3.30† years), we see that growth is 61.5 per cent and weight 18.3 per cent complete. At 16 years growth is 90 per cent achieved though weight is merely 64 per cent fulfilled. Beyond 16 growth is negligible indeed, though increase in weight continues normally until much later. These estimates, in conjunction with the curves, show clearly that, for the period succeeding the obligative intrauterine stage of life (Fig. 2) growth accumulates in greatest quantity during the circumnatal epoch. Under ordinary conditions we have the opportunity of observing this only during normal infancy, and the latter, accordingly, becomes the period of postnatal growth *par excellence* just as it is commonly held to be.

But, interestingly enough from the standpoint of the present discussion, we are apt in the routine course of events to think of infancy as the

*In reading this section devoted to the differentiation between growth q and weight z, it will probably be helpful to recall, in addition to the brief definitions of Table I, that growth q explicitly takes account of the quantity of tissue which is responsible for generating the resulting change in size. If we remember, moreover, that rate of growth = rate of reduplication under the conditions stipulated in a footnote to Table I, it is clear that quantity of growth must be equal to quantity of reduplication and hence, more generally, "to change in size per unit size."

†The final "0" is significant, the correct value to three decimal places being 3.301.

"grand" period of growth almost certainly from considerations of change in weight (z) rather than because of actual changes in growth itself although these, as we now see, are even more strikingly displayed

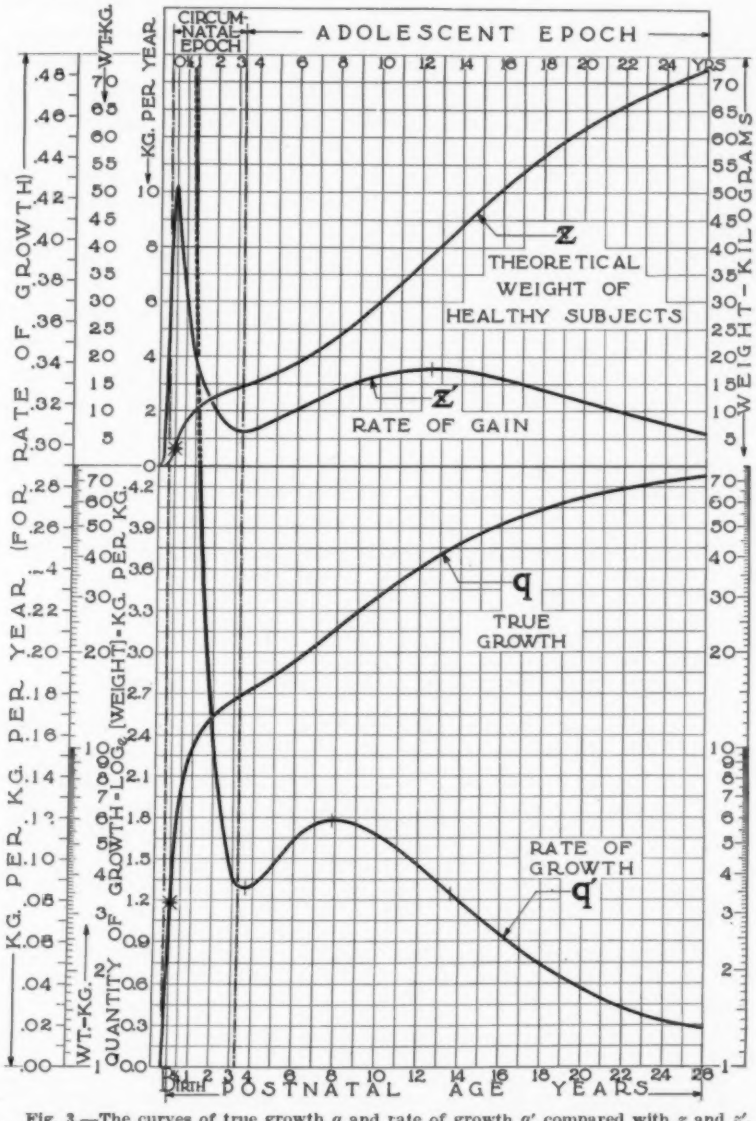

Fig. 3.—The curves of true growth q and rate of growth q' compared with z and z'. A thread or straight-edge leveled with the aid of the two logarithmic scales will enable the equivalent values for weight along q to be read at a glance. The scale for quantity of growth is divided with reference to 1 Kg. at the start, that is, at the 190th day or just 17 days beyond the line of demarcation in Fig. 2. If reference on the basis of 1 gm. be desired, it is necessary to add 6.9078 to all values on this scale.

by q. This comparatively awkward situation is due to the fact that we do not and cannot measure the quantity of growth directly. In practical work we are required instead to deal explicitly with size or change in size (z), and we think most readily in terms of this secondary attribute of growth. It is extremely important to keep the foregoing distinctions clearly in mind, for certain phenomena, especially those which touch immediately or even remotely upon nutrition and metabolism, will, by their connection with growth, likewise prove to be pertinently related to growth itself rather than to cumulative change in weight.

*Rate of Growth q' and Rate of Gain z'.**—The changes in q' during the earlier phases of life again exceed in degree the corresponding changes in z'. Here the more conspicuous difference is to be found in the unlike trends exhibited by rate of gain on the one hand and by rate of growth on the other. Whatever similarity they possess is associated with the fact that both curves descend to, and pass through, a minimum point; that they do so almost but not quite simultaneously at 3.30 and at 3.65 years (postnatal age), respectively; and that they reascend to individual maxima which are situated at rather widely separated points, the earlier being at 7.85 years for the rate of growth, the later appearing at 12.48 years in the rate of gain. With the exception of these particular characteristics they have little else in common; q', for example, descending continuously throughout prenatal life from extremely high original levels† to reach the comparatively low values of:

3.1208 Kg./Kg./Year at birth;
0.3788 Kg./Kg./Year at 1 year; and
0.0861 Kg./Kg./Year at the minimum point (3.65 yr. postnatal time);

only the latter two of which are represented on the curve, q', of Fig. 3. But the rate of gain, z', as previously noted, pursues a course quite opposite to this, and rises during the prenatal phase to the first of its two

*D'Arcy Thompson in a celebrated passage[29] has criticized Minot's[30] method of approximating the value of what the latter was among the first to recognize clearly as the rate of growth (herein symbolized by q'). Apart from the question of method, Thompson had real misgivings about the advisability of turning to logarithms and their auxiliary relations in order to define growth because this procedure "could only be defended and justified if it led to some simple result, for instance if it gave us a straight line, or some other simpler curve than our usual curves of growth." Davenport[4] has also doubted the justification for the use of logarithmic curves although he has done so on quite different grounds. His criticism is directed against them primarily because their differential equation, as ordinarily written in its simplest form, provides explicitly that rate of gain be proportional to weight at any and every instant, a condition which stands in conflict with his earlier results on frog embryos to the effect that "not all the body substance is growing substance"[31] in virtue of imbibition of water. If the reader will follow Poincare's suggestion "to generalize"[32] and will then accept our broad definition that growth is "change in size per unit size," he will likewise find that "quantity of growth" is not only conveniently but also necessarily a logarithmic function of size (weight), irrespective of whether the resulting curves turn out to be simple or complex. He will find, in addition, that a recognition of this fundamental logarithmic nature of growth is of indispensable assistance in arriving at the direct connection between the events of growth and those of concomitant heat production or metabolism.

†Between the thirty-fifth and one hundredth day of gestation this rate drops from about 30 to 16 Kg./Kg./Year. Were the average of these values to persist from the one hundredth day of gestation (i.e., when weight = 0.069 Kg.) to "term," the resulting fetus would weigh 5,825 Kg. or 12,815 pounds and would be gaining approximately 367,000 gm. per day!

great maxima which coincides in time with birth. The latter curve is then reversed and proceeds to descend simultaneously with the rate of growth until their respective minima at 3.30 and 3.65 years are individually reached.

The rate of growth, moreover, passes through but one maximum point just before 8 years, this, in fact, being situated some 4½ years in advance of the second maximum in z'. It then falls off with increasing rapidity until the point of inflexion at 13.6 years is penetrated where the value of q' is just short of that at its minimum some 10 years previous. The curve finally descends at continuously decreasing rates although always more rapidly than the comparatively sustained fall in the rate of gain; the latter, for example, at 20 years being approximately 23 per cent of its birth value, whereas the rate of growth at the same point represents but 1.2 per cent of its own "original" value at birth.

In summing up the foregoing comparisons between growth and gain from the clinical point of view, several results stand foremost: (1) that the "grand" period of growth as portrayed by q and q' comes to a close with the passing of infancy; (2) that the succeeding minor episode of adolescence is likewise all but complete before the outward evidences of puberty most usually appear; (3) that certain well-recognized and important physiologic or developmental events take place simultaneously with the transits of growth and gain across the several critical points herein described; and (4) that growth differs significantly from year to year because it is characterized at one stage by a concomitant rise or drop in the rate of reduplication and in the rate of gain, but at other times by oppositely directed trends in these two fundamental items.*

Comment.—Before leaving this particular phase of the subject where so much emphasis has been placed upon the distinction between growth q and cumulative weight z, between rate of gain z' and rate of growth q', as well as upon their individual trends throughout life, it would be well to consider a few additional matters which bear directly upon the validity of these curves and hence upon their clinical interpretation. How much, for example, can we depend upon the results already illustrated that the minima in z' and in q' occur at 3.30 and at 3.65 years respectively? To what extent are we justified in placing the maxima in the rate of gain at birth and at 12.5 years following this, or finally, in stating that the only maximum in q' is located at 7.85 years, it being understood that the foregoing critical points belong solely to, and are characteristic only of, the curves now under consideration, and that the latter represent merely the major deflections found in the curves of individual healthy children?

To begin with, it must be noted that z, z', q, and q' may be computed to any desired degree of numerical precision from the original equations

*Rate of growth q' and rate of gain z' are necessary, though not sufficient, for defining states of growth or their changes with age. To obtain a more complete description we should compare all the items in Table I.

of motion[1] which have been applied for this purpose directly to, and have been found, as Figs. 1 and 2 show, to conform with suitable data on human weight from early fetal to adult life. For this reason a fair degree of confidence may here be placed in the foregoing results. But even though the period over which these equations hold true is exceptionally long, we have not relied exclusively upon the single criterion that they represent change in weight z or growth q alone. As we shall see in the next section, additional confidence may be placed upon the present results because the components of z, z', q, and q' likewise define the corresponding trends of human basal heat production with equally great fidelity. Growth and basal metabolism thus being directly related, we may expect, in virtue of this dual connection between data of quite independent origin, that any individual estimation will be proportionately more trustworthy.

When we assume to describe the natural course of human growth by means of z, z', q, and q', and further, to stipulate that the minimum of z' is at 3.30 years, whereas that of q' is placed at 3.65 years, and that the maximum of the latter is at 7.85 years; it is clear from what has just been said that we are taking few if any liberties with numbers. Once q and z are set by the double criterion of growth and heat production, the matter of determining the peaks and troughs in q' or in z' becomes merely a problem in numerical computation. Even in spite of this precaution of not relying upon a single source of values (z) for the application of our hypothetical equations of motion, there is, and there will always remain within the allowable limits of biologic variation a certain, and perhaps indeterminate, doubt as to the exact trends already discussed. The problem and the results depend in the last analysis not so much upon the equations we have proposed, for these, as is even now evident, are quite clearly capable of representing growth, and they represent, likewise, the course of human basal metabolism shortly to be described. Such deviations as may occur between the present and the "true" values will not (at least they should not) be due to numerical errors; they will depend only upon the proposition that it is impossible in general to obtain a result more accurate than the original data themselves allow.

Consequently, wherever the statement is made that the rate of growth passes through a minimum at 3.65 years and subsequently rises to a maximum at 7.85 years, it is intended to represent only as numerically accurate a result as could be obtained from the data we have selected. Other data might easily have given somewhat different values. For example, compare Scammon's[33] careful computations of what we prefer to call the rate of growth, that is q', which are based upon the records of Emerson and Manny.[14] The general shape of Scammon's curve is almost precisely that for q' shown in Fig. 3; but he finds the minimum in Emerson and Manny's data to be situated closely in the neighborhood of

eight years, that is, at about the very point where our results quite clearly indicate a maximum instead. The maximum in his curve is likewise displaced farther to the right and is located near the 11- to 12-year mark although from that point on, as well as for the period between birth and four years, no remarkable difference between Scammon's curve and that of Fig. 3 can be found. In contrast with these differences in contour, it may be said that the average level of the two curves is practically identical even during the 4-to-12-year period, in which their shapes are clearly unlike. In comparing, but especially in attempting to interpret such differences, it is well to remember that the determination of maxima and minima from a set of experimental data which display the degree of scatter usually found even in weights of normal subjects, is at best an extremely precarious task. The results are bound in the nature of the case to be somewhat more suggestive than final although the chief cause of any difference between estimates of critical points can be traced to deviations which exist in the data themselves. The question, as to whether Scammon's or our own value for the age at which the rate of growth passes through its minimum is more nearly correct, thus resolves itself into one of determining whether the observations of Emerson and Manny can be said to represent the "general course of human growth" as accurately as they portray the trends of their own special group of children. These things being so, we are here inclined to the view that the rate of growth, in the great majority of healthy children, reaches its minimum during rather than after preschool life, and that the point itself is closely in the neighborhood of 3¾ years. Support for this comes primarily from the facts: (1) that the present results have been obtained by applying our equations to data drawn from widely separated sources rather than to those collected on a single group of subjects; (2) that the equations hold true from the earliest measurable fetal stages to adult life; and (3) that these "theoretical" results for weight are completely in harmony with entirely independent data on basal heat production.

The year between the ages of three and four thus becomes doubly significant in view of the fact that both the rate of gain as well as the rate of growth are at their minimum here. Clinicians will recall this as the very period in which other great physiologic changes characteristically take place, the "second crossing" of lymphocytes and polymorphonuclear cells in the blood and the completion of the first dentition. The former of these events is excellently illustrated in a recent monograph by Brock,[34] as well as in the older work of Feldman.[35] But the great importance of preschool life as a period of transition and hence as a period of readjustment is even more forcibly emphasized by turning next to a consideration of the corresponding age changes in basal heat production.

Corresponding Curves of Heat Production
[*Fig. 4, (Uz) and U*]

We shall study this equally important phase of the problem of growth and metabolism by means of curves (*Uz*) and *U* in Fig. 4. The upper represents the trend of basal heat output in terms of *Cal./Day*, the lower in terms of *Cal./Kg./Day*. Each of these rises rapidly during the first year (in contrast to the equally steep descent of the curve representing the rate of gain) to reach a somewhat different type of peak at or just after the end of this first year. The curve for daily heat output (*Uz*) then descends unmistakably, though not greatly to a minimum located at about 3.30 years, the drop during this period being just less than a 100 Cal./Day. But the curve for heat production in terms of Cal./Kg./Day, *U*, descends to the boundary of the circumnatal epoch almost as sharply as it had previously risen to its peak, thenceforth continuing in a shoulderlike descent, (at an extremely low rate up to the age of six) whence it turns downward again into a more definite fall to approach closely to the "equilibrium" or maintenance level at about 24 years of age. The latter remains constant, or better perhaps, it is assumed from the dynamic side of the problem to remain so throughout life, the excess of heat output above this being entirely due, as we have elsewhere described in greater detail,[2] to the overload of growth itself.*

Each of the foregoing curves thus represents the trend of basal heat production in its own particular unit, Cal./Day and Cal./Kg./Day, respectively. Each may be, and has been taken, as an expression of the age change in "basal metabolism." But to do so indiscriminately will lead to confusion and even to serious error in clinical work. We meet, for example, with the statement that basal metabolism declines with age. This, obviously, could apply solely to the lower curve, *U*, representing heat production in *Cal./Kg./Day*, and then only for the period succeeding the first year. Yet sooner or later we encounter the declaration that energy requirements and heat output are proportional to weight (or to body surface, either real or effective), and we are therefore required to infer that "metabolism" increases with advancing years. Clearly, the

*More directly illustrated in Fig. 5 where the area between the maintenance level and the curve for *U* in Cal./Kg./Day represents the quantity of heat held to the account of growth. This portion is itself the sum of "heat of dissipation" and "heat of cellular synthesis" (proliferation) as previously described,[2] and vanishes when growth has ceased. The comparatively high metabolism of infants and children is therefore directly to be attributed to the fact that "they are immersed in the flux of growth"[2] in contradistinction to the quite unsatisfactory though traditional explanation invoking the surface law.

It has been interesting while preparing this paper to learn that Fleming[28] expressed somewhat similar views, a decade ago, and he is, so far as we are aware, the only writer on the subject to have suggested unmistakably that the high metabolism of childhood may be due to growth itself. He undertook to demonstrate this by a method of computation equivalent to approximating the area between *U* and the maintenance level in Fig. 5; and the results "seem to afford," he says, "a certain amount of evidence in favor of the suggestion that the high basal metabolism of the growing child may to some extent be accounted for by the amount of energy expended in the manufacture of new tissue." This is, clearly, quite a different point of view from that of other workers who ascribe high metabolism in infancy and childhood and its subsequent fall merely to an age change, or just as unconvincingly, to the hypothetical effect of a diminishing ratio between surface and mass as age advances.

latter could be true only of the upper curve (Uz) defining the course of heat production simply in Cal./Day.

What is the cause of, and what the remedy for the paradox? We have already discussed the matter in a preceding paper,[2] but it is useful in connection with the present description of the curves in Fig. 4, and also

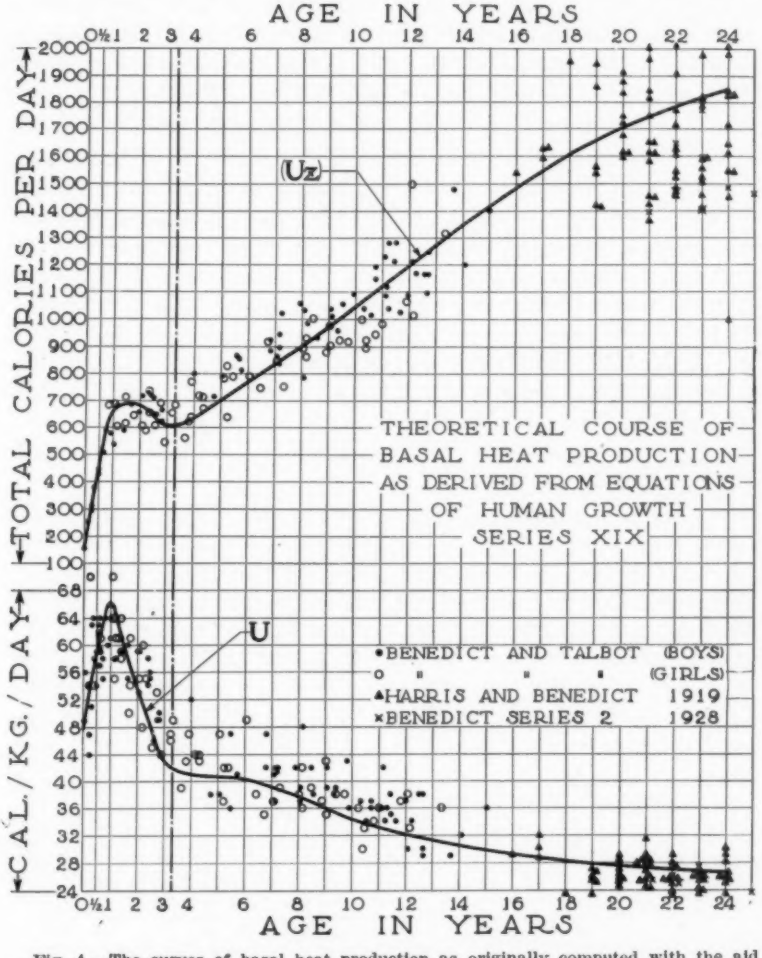
AGE IN YEARS
TOTAL CALORIES PER DAY
CAL./KG./DAY
Uz
U
THEORETICAL COURSE OF BASAL HEAT PRODUCTION AS DERIVED FROM EQUATIONS OF HUMAN GROWTH SERIES XIX
•BENEDICT AND TALBOT (BOYS)
○ " " " (GIRLS)
▲HARRIS AND BENEDICT 1919
×BENEDICT SERIES 2 1928
AGE IN YEARS

Fig. 4.—The curves of basal heat production as originally computed with the aid of the accompanying data indicated in the legend. The observations of Topper and Mulier,[36] Göttche,[37] and of others are not included (though they follow these curves very well over their respective periods) because our equations were applied in the case of Series XIX solely to the data of Benedict and his coworkers.[9]

because of the rather considerable practical importance in having a clear understanding of the point, to inquire into the chief elements which contribute to possible confusion here.

The situation is briefly this:

The term "metabolism" refers to the sum total exchange of energy in the basal state as judged conveniently by measurements of heat production. Thus, "metabolism" and heat production become conceptually related, but, since the latter is sometimes recorded in terms of *Cal./Day* and at other times as *Cal./Kg./Day*, it is easily possible to be led into thinking of metabolism in terms of either quantity interchangeably, the foregoing conflict being an almost inevitable result. The units themselves are, of course, equally valid; it is rather a question as to which is more appropriate. Two considerations come into play. There is, first, inherent in the basic idea of metabolism a tacit suggestion of reference to time, as well as to size; second, there is the purely practical problem of dealing with subjects of varying age, and hence of varying size, throughout the period of childhood growth, in addition to the problem of considering the natural deviations in size among children of the same age. It is, accordingly, held desirable to make comparisons of heat production in relation both to size and to time, i.e., *per Kg.* and *per day*. Thus we see clearly that "metabolism" is more suitably expressed in terms of *Cal./Kg./Day*, the choice of mass as a measure of size being favored, as elsewhere pointed out,[2] on the ground that this, rather than surface area, is the more convenient, as well as the more appropriate unit, in which to evaluate changes in growing subjects.*

In spite of this full theoretical justification of regarding "metabolism" as heat production preferably in Cal./Kg./Day, it turns out, somewhat unfortunately, that we must expect (from the mathematical connection between growth and heat output[1, 3]) considerably less uniformity in data recorded in Cal./Kg./Day during the period of growth than in those expressed simply in terms of Cal./Day.† It can easily be shown from the same equations that the relative error in the former unit, engendered by a deviation in weight, will be about twice as great for any subject undergoing growth as the corresponding relative error in the latter. Where

*It will have been noted that we do not follow the widely prevalent clinical custom of defining daily rate of heat output per unit of size (Cal./Kg./Day or Cal./Sq.M./Day) as "metabolic rate." Such usage, strictly speaking, is incorrect since the quantity in question is not simply a rate but is rather a rate qualified per unit size. If it be found desirable to retain the phrase "metabolic rate," it will be necessary to select one of two possibilities: (a) to define daily heat output as such or (b) to specify explicitly "basal metabolic rate per unit of weight" or, when reference to surface is preferred, as in Bruen's paper,[2] "basal metabolic rate per unit of surface." Each of the terms in (b) reverts, incidentally, to the definition given in (a); each possesses the theoretical advantages discussed in the text, and each would be satisfactory if consistently employed. The danger, however, is that the comparatively unwieldy terms in (b) would again be abbreviated to the incorrect form "metabolic rate." These remarks afford further evidence for our own reasons in advancing the suggestion that the transactions of energy exchange, conveniently regarded as "metabolism," be thought of in terms of Cal./Kg./Day. There should be no more difficulty in doing so than in accepting the speed of a train implicitly as miles per hour, with the result that the dilemma of names otherwise engendered is automatically escaped. To us the most convincing argument in favor of the definitions we suggest comes from the fact that the equations of growth take their simplest form when each term has the same physical dimensions as "metabolism," namely, power per unit mass. From the dynamic standpoint (rate of energy expenditure per unit mass) growth and metabolism may therefore be considered as homogeneous transactions.

†An excellent illustration of this principle is to be seen in some recent curves on heat production in undernourished children reported by Topper.[4]

growth has ceased, or has become negligible, and hence, where basal heat production is due simply to "heat of maintenance"[2] (i.e., where $U = A' = 25.34$ Cal./Kg./Day), we must expect instead to find much greater uniformity in values expressed in Cal./Kg./Day.

This curious though highly important situation whereby the two foregoing units of measure are characterized at different ages by precisely opposite degrees of reliability is explained most simply as follows: Taking the more common methods of expressing heat output, Cal. /Day and Cal./Kg./Day, and recalling that heat production during growth is due in part to growth and in part to "heat of maintenance,"[2] we have, literally, in accordance with the symbolism of Table I,

$$\text{Item 7: } (Uz) = \begin{matrix}\text{Daily Rate of Heat} \\ \text{Production}\end{matrix} = \underbrace{\left[\begin{matrix}\text{Heat of Growth}\end{matrix}\right]}_{\begin{matrix}\text{Involves Weight } (z) \\ \text{inversely}\end{matrix}} + \underbrace{\left[\begin{matrix}\text{Heat of Mainte-} \\ \text{nance}\end{matrix}\right]}_{\begin{matrix}\text{Involves Weight } (z) \\ \text{directly}\end{matrix}}$$

and

$$\text{Item 8: } U = \begin{matrix}\text{Daily Rate of Heat} \\ \text{Production per Unit} \\ \text{of Weight}\end{matrix} = \underbrace{\left[\begin{matrix}\text{Heat of Growth} \\ \text{per Unit Weight}\end{matrix}\right]}_{\begin{matrix}\text{Involves Weight } (z) \\ \text{inversely as the} \\ \text{square}\end{matrix}} + \underbrace{\left[\begin{matrix}\text{Heat of Mainte-} \\ \text{nance per Unit} \\ \text{Weight} = A'\end{matrix}\right]}_{\begin{matrix}\text{Independent of} \\ \text{Weight}\end{matrix}}$$

It will be clear from a study of the preceding scheme that item (8), heat production in Cal./Kg./Day, (U), must be more at the mercy of deviation in weight (since it involves the square of weight inversely) than the corresponding unit, item (7), Cal./Day, in which the inverse action of weight as regards heat of growth is bound for practical purposes to be fairly well counterbalanced by the direct entry of weight into the fraction due to maintenance. This, precisely, is the case when growth is not negligible; but, when growth has ceased, the portions resulting from growth must vanish, and it is clear that the foregoing relationships then become simply,

$$\text{(7a): } (Uz) = \left[\begin{matrix}\text{Daily Rate of Heat Pro-} \\ \text{duction}\end{matrix}\right] = \underbrace{\left[\begin{matrix}\text{Heat of Maintenance}\end{matrix}\right]}_{\begin{matrix}\text{Involving Weight } (z) \\ \text{directly}\end{matrix}}$$

and

$$\text{(8a): } U = \left[\begin{matrix}\text{Daily Rate of Heat Pro-} \\ \text{duction per Unit of} \\ \text{Weight}\end{matrix}\right] = \underbrace{\left[\begin{matrix}\text{Heat of Maintenance per} \\ \text{Unit of Weight, } A'\end{matrix}\right]}_{\text{Independent of Weight}}$$

In the latter circumstances, accordingly, heat output in Cal./Day is alone bound to suffer in respect of deviations in weight; the results in terms of this unit will therefore vary more widely, show greater scatter

when plotted, and will appear less uniform in comparison with data registered in Cal./Kg./Day because the latter is now, in the absence of growth, altogether independent of weight so far as the generation of heat is concerned.*

The foregoing theoretical results are clearly demonstrated by the respective curves in Fig. 4 since the adjustment of (Uz) to the data is visibly better than that of U from birth to 16 years, whereas following this we actually find the reverse to be true.† Similar statements apply to observations on heat production in other organisms.

We are therefore faced in clinical pediatrics with the problem of evaluating the disadvantage of adhering, for the sake of consistency, to a unit of measure (Cal./Kg./Day) which, on the one hand, is itself theoretically desirable, but which, on the other, is always subject, where growing children are concerned, to a comparatively large relative error in practice; or, of dealing with the simpler unit, (Cal./Day), which suffers in turn from the theoretical defect of relating heat output solely to time, rather than to size as well as to time. Circumstances here, as elsewhere, are obviously bound to affect the final choice; but in summarizing this discussion it would seem fair to say that we ought, in working with such data, to consider the merits of these two units carefully, bearing in mind that the simpler unit, Cal./Day, is inherently subject to the lesser error during the entire period of growth; whereas, in speaking of "metabolism," we ought to reserve the use of this term specifically for

*It is necessary in such considerations to distinguish clearly between two fundamentally different issues: (i) the reliability of a result *as based upon actual computation* from the experimentally observed values of heat output, and (ii) the expected reliability *as based upon the generation of heat* in virtue of the dynamic connection between growth and heat production. The latter is subject to errors that occur in the basic data, the former to error that is imposed *upon* them. With regard to (i), a result calculated as Cal./Day from suitable measurements in calories that are then estimated for the 24-hour period is independent of weight so far as actual computation is concerned and it is therefore "free" from "error" due to weight. Turning to view the problem from the causal standpoint (ii), as we do in the text above, that a child of z Kg. growing at the rate of q' Kg./Kg./Day generates (let us say) y calories of heat in unit time; we find instead, just as outlined, that daily rate of heat production (Uz) is actually a function, on dynamic grounds, of $\left[\frac{1}{\text{mass}}\right]$, whence U must obviously be a function of $\left[\frac{1}{(\text{mass})^2}\right]$. Taking mass in terms of weight, both quantities thus become susceptible to error resulting from deviation in weight as long as growth persists. The reliability of any final result, so far as deviation in weight is concerned, will therefore be determined (discounting all technical discrepancies) in part by "error" arising, out of (i) and in part by "error" from (ii); whence values in Cal./Day will suffer, during growth, only from an "error of generation" (ii) inherent in the measurements themselves, whereas final values in Cal./Kg./Day will carry both the "error in the data" as well as that of (i) imposed by computation. Thus, in either instance, U is seen to be more susceptible than (Uz) to deviations in weight as long as growth continues.

It must finally be remarked that the foregoing distinctions and results can be numerically corroborated only in data collected with the highest possible technical precision. In the latter respect no published observations exceed those of Benedict and Talbot,[9] or those of Du Bois[12] and few compare with them. It is consequently not to be expected that results obtained in ordinary routine clinical work will be sufficiently accurate to display these differences so strikingly.

†Had the observed weights in the corresponding data of Fig. 4 not differed at all from the theoretical weights as given by z in Fig. 1, we should have found the adjustment of U to be just as good as that of (Uz) from birth to 16 years, any scatter still remaining along either curve during this period being due solely to technical differences in the measurements of heat output. Thus, since U would be shifted more than (Uz), it is again evident that the former is the more sensitive to deviation in weight.

heat production as related both to time and to size. When so defined, it is no longer possible to mistake the meaning of the statement that metabolism tends to decline with age.

Changes in Weight, Rate of Gain, and in Basal Heat Production Referred Simultaneously to Age

By way of summary it will be useful with the aid of Fig. 5 to review the age changes of "growth" together with those of "metabolism." Comparison is again made directly with respect to the more familiar trends of weight and rate of gain although it will also be well to keep in mind the corresponding phenomena of growth itself as already described in connection with Fig. 3.

The two epochs, circumnatal and adolescent, are dominated by the deflections in the curve displaying the rate of gain, z', and the transition between these epochs is clearly indicated by the "trough" of velocity which thus marks out the period of relaxation in "growth" associated with, and even peculiar to, the age of preschool life. While it is true that special characteristics appear in all of the curves at this time and that these clearly indicate the preschool pause in gain and in basal heat production, it may also be remarked that the slowly shifting changes between 1½ and 4½ years are least distinctive in the weight curve, the very one, in fact, upon which we are compelled for the most part to depend in the usual routine of clinical work. The critical nature of this period is excellently brought out in the curves for heat production, though it is illustrated best by the "double inflexion" in the upper graph, (Uz), the minimum of the latter at 3.30 years being coincident with that in the rate of gain. A striking array of fundamental physiologic events thus combine to stamp the preschool period as one of great transitions; critical changes in growth, gain, and in heat production are coupled with the equally significant changes in the blood at a time when the first dentition has just been completed and when the brain is almost fully developed. There can be little doubt that this is just as important a phase of childhood as the periods in which the rate of gain rises to, and passes through, its two great maxima.

CLINICAL SIGNIFICANCE OF CERTAIN EVENTS DURING THE FIRST OF THE TWO MAJOR DEFLECTIONS IN THE RATE OF GAIN AND IN THE PAUSE BETWEEN THEM

Circumnatal Epoch

There are several outstanding practical problems with which a pediatrician is bound to be concerned when dealing with subjects in this stage of life. Taking these in chronologic order, we meet first the problem of growth in the premature baby, the physiologic loss of weight at normal birth, and lastly the matter of gain, or rate of gain during early

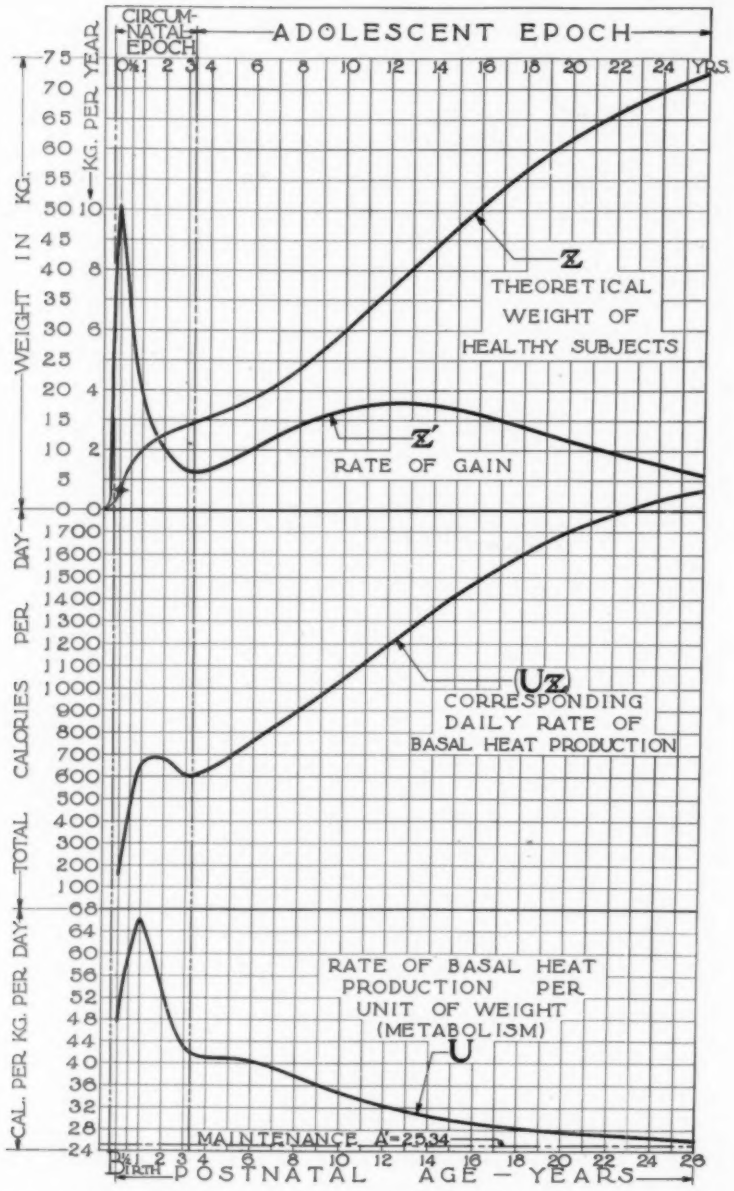

Fig. 5.—The theoretical trends of basal heat production compared with weight and rate of gain. It may be observed in the lower section that the area between *U* and the maintenance level represents the portion of heat in Cal./Kg./Day which is produced by, and is due to, growth.

infancy. Worth noting here, though not of direct practical significance, is the fundamental biologic problem of the "cause" of birth; for it is not without interest that the normal full-term child should be born at the very peak of its rate of gain as shown in curves z' of Figs. 1, 3, and 5.

Prematurity.—It is now somewhat simpler to understand, in view of what we have just noted, why the care of a premature infant should be proportionately more difficult than that of the full-term child, other things remaining approximately the same.

The chief difficulty, of course, is its want of "ripeness," here expressed and represented in the fact that such an infant is endowed with the propensity of climbing to its succeeding peak velocity,* which is naturally scheduled to take a month or so beyond but is required to attempt this under conditions that are removed from the favorable circumstances of intrauterine existence. It is not common, as far as present records on the subject go, to have the smaller premature babies traverse a course of gain in weight at the rates here indicated for the latter portion of fetal life. Such gains, in the case of a 1,000 gm. premature infant, would call for reduplication in weight within forty-four days of its birth, and the resulting weight curve could be directly superimposed upon the respective segment in Fig. 2. Sufficient experience has already accumulated to show that this curve can be very closely approximated under certain special conditions of feeding and care. Real emphasis must be placed upon the point that the difficulties of rearing premature infants are occasioned largely, if not entirely, by the dynamic stresses of growth which these infants are required to withstand and to overcome under the comparatively adverse conditions of extrauterine life. No food, however well chosen, can eliminate such stresses as these which arise during periods of "natural" or "intrinsic" acceleration in the rate of gain. Proper feeding and careful hygiene for premature infants will do much to minimize the additional risk that this particular burden of growth implies.

Physiologic Loss of Weight at Birth.—If the several curves we have now been investigating had been drawn simply by eye through the respective data each represents, it would have been necessary to include at birth a slight but definite break, or downward deflection in the curve for weight, z, followed by a two-week period of recovery. To correspond with this, the velocity curve, z', would have shown a similar, though greater change (on the basis of scale), and would even have fallen below zero during the period of loss in weight, only to rise to the peak already shown when "growth" had once more become reestablished at the end of the "neonatal" period. The two curves in question have been obtained by a different method, and they represent in continuous fashion what may, for theoretical purposes at least, be considered the "ideal" tendency and

*Dynamically equivalent to peak momentum per unit length.

trend of these two special aspects of human growth. The "physiologic" loss of weight in the newborn does not appear in them; and it fails to appear because the equations from which these curves have been computed are based upon the assumption that nutriment is just as available to a newborn infant as it is throughout the entire course of growth. Since this is usually not the case at and for a short time after birth, it is necessary from the dynamic point of view to regard the physiologic loss of weight as an accidental and not as a fundamental event in the clinical careers of all newborn babies. Sufficient support for this conclusion is to be found in various studies on the point,[11, 41] for it has been shown that loss of weight at this time can be prevented when infants tolerate the required quantities of food.* But the clinical advantage of doing so is certainly a questionable one, chiefly because the onset of lactation may be considerably delayed. Such attempts, as Shick[41] has remarked, are more than likely to be superfluous, for the milk supply is soon established under ordinary circumstances and normal gains quite promptly ensue.

Rate of Gain in Weight During Infancy.—From our own studies[1, 2, 3] we have come gradually but definitely to the conclusion that there is no problem of infantile growth which merits more consideration on the clinical side than that pertaining directly or indirectly to the rate of gain. There is a well-known tendency in some quarters to regard this particular aspect of growth indifferently although it cannot easily be denied that the almost universal practice of some kind of regulation in the quantity, number, and time of breast or artificial feedings is carried on, whether explicitly or not, through the realization of the fundamental importance of promoting normal and of preventing abnormal gains.

The results to which we refer speak strongly in favor of deliberate moderation in the matter of raising big babies. Consider once more curve z' in Figs. 1 and 5. Close examination here shows that this curve rises practically from zero in the early days of gestation to the value of 10.146 Kg. per year, or 27.80 gm. per day at birth. Succeeding this, except for the physiologic loss already discussed, the rate of gain falls swiftly (on the annual basis of time) to the value of 17.97 gm. per day at six months and to 10.45 gm. per day at the end of the first year. These values agree with an old pediatric rule of the thumb to the effect that a normal baby should gain, on the average, an ounce a day during the first six months and about half an ounce a day during the second six months of life. But experience shows that, in spite of this axiom, many parents and a goodly number of physicians as well still take an unjustified pride in great and rapid gains. We see all too frequently a baby whose record is marred by gains of 10 or 12 ounces and even more per week. Such an infant, up to the moment of examination, has

*Compare also MacDowell's[42] interesting observations on the part which a limited supply of food plays in determining gain in weight among newborn mice.

usually escaped the certain fate that succeeds excessive increments of weight, and it is chiefly on this account that both physician and parent are apt to treat the problem lightly.

What are the objections that may be raised against the practice of allowing infants to gain more rapidly than the traditional canon allows? Leaving the well-known clinical and pathologic consequences of overfeeding quite aside (since the latter is by far the most common cause of excessive gain in early life), there are, in reality, two important disadvantages which are forcibly brought to our attention from the dynamic side of the problem. In the first place, abnormally high rates of gain are bound to be followed by equally abnormal low rates of increase, and they may indeed be succeeded by periods of actual loss as well. Experience itself has sufficiently substantiated this, but the result may likewise be easily demonstrated by the following consideration.

The area enclosed by the velocity curve z' Fig. 5, is exactly equal to the actual weight z at corresponding points or ages, the total area thereunder being the final adult weight. If we distort this curve in any portion, for example, along the segment covering the first six months where excessive rates are most frequently witnessed from overfeeding, it must clearly follow, to keep the total area the same, that an equivalent distortion in the direction of a lower velocity must subsequently be introduced. The normal period of adjustment already noted and described as a period of comparative rest and preparation for the secondary climb in later childhood, is thereby unavoidably lengthened; compensation, even in the matter of velocity, is unescapable. Witness the infant who doubles his weight in the first three months and then fails to gain even normally, in spite of efforts to the contrary, until "age has caught up with weight."

Thus far we have counted the cost of great gains merely in terms of a subsequent, needless delay in "growth." But a second, and to us, an even more important disadvantage on dynamic grounds is to be found in the fact that doubling the rate of growth, i.e., the relative rate of gain (Table I), creates when other things remain the same, a fourfold increase in that portion of energy which is necessarily dissipated per unit of time in every instance of growth even under natural or more normal conditions of reduplication. The energy so dissipated appears in the form of heat and tends thereby to raise the basal metabolic output of heat correspondingly.[2] What physiologic devices there are to neutralize this waste we do not know, nor can we be sure that harm will not be done by stimulating rates of gain exceeding those which long experience justly considers optimal in the human case. Thus, as our studies suggest, it would appear unquestionably better to avoid these difficulties entirely, if for no other reason than to prevent a "growth fuse" from burning out.

We come therefore to three major conclusions, in respect of rate of gain, which may be summed up as follows: first, that it is unnecessary

to promote a gain of more than an ounce a day on the average at any time of life, and to expect that rate only during the very first trimenon; second, that excessive rates of gain will be followed by periods of delay in growth; and third, that such rates are accompanied by, and give rise to, even greater rates of energy dissipation. These conclusions are reached from a study of the dynamics of growth; but they cannot, obviously, be applied on the clinical side without full recognition that equally healthy infants differ greatly, and that such differences cannot be entirely disregarded in the problems of their individual care.

The emphasis which has just been placed upon the dynamic importance of preventing excessive and of encouraging normal rates of gain requires a final word of comment. A counter objection might, for example, be raised to the effect that recent studies in the nutrition of white rats[43] have shown no demonstrable difference between animals forced to gain at a rate twice that considered by modern practice to represent the normal for the species. Health, development, and the common "anthropometric" measurements of the two groups were the same, no objective differentiation between them having been found possible. On this ground alone, there might be reason to believe that rate of gain per se could be disregarded in the matter of infant feeding. Yet, neglecting several important differences in the two cases under examination, we know it is well from the clinical side to recall the familiar rule that, in the last analysis, the human baby, and not the rat, must be the subject of any such *experimentum crucis*. From the theoretical side we should be justified, perhaps with greater reason, in suspecting that normal growth in rats requires further investigation. For it is quite unthinkable that the usual maximum rate in the human case, 1 ounce per day, could be doubled and maintained over any significant interval at the level of 2 ounces a day without leading to a "break"; whence, in judging the comparative ability to withstand the strain of distorting their respective curves of rate of gain, we should be required to conclude that the standards of optimal growth for the rat and for the human infant are, as yet, not strictly comparable. Even though they were, it would still be necessary to regard most seriously the striking fact that the normal maximum rate of gain in the human case is slightly less than an ounce a day. On dynamic grounds at least, there is no need, and we are obliged to add, still less wisdom in attempting to exceed this rate. From the purely practical side of the matter it is sufficient to remember only the simplest and indeed safest rule of all, namely, that no infant requires to gain more than one ounce a day to assure its full attainment of growth.

Preschool Pause

This period, as already mentioned in an earlier section and as shown in Figs. 1 to 5, extends somewhat in either direction from the line of demarcation between the circumnatal and adolescent phases of growth.

Its conspicuous characteristic, as the name implies, is the halt in the velocities of gain and growth as shown by curves z' and q' although each of the other three curves likewise passes simultaneously through a period of comparative rest. This is of definite clinical importance, for it has not always been clearly recognized that gain, and hence growth, slows down remarkably here. Since there is an even greater change in the trend of basal heat production during the period in question, it will be better to discuss the preschool pause from the latter standpoint.

The Leveling-Off in Basal Rate of Heat Production from 1 to 4½ Years.—Attention has already been drawn to the curious "double inflexion" between the ages of 1 and 4½ years in curve (Uz) of Figs. 4 and 5 representing basal heat output in Cal./Day. The maximum value is reached at approximately 18 months and the succeeding minimum at about 3.30 years, the total variation between the two extremes being something less than 100 Cal./Day. In spite of this completely unexpected result in our original computations we found, as Fig. 4 shows, that the data of Benedict and Talbot[9] were distributed nicely about the entire curve and notably so over the interval just now under examination. The exact trend of the curve depends upon certain mathematical relations between growth and simultaneous heat production; but it is clear, if we consider the technical difficulties in making observations of heat production on subjects of this age and allow for unavoidable scatter in the results, that the complicated course of the curve during preschool life could hardly be traced on the basis of experiment alone.* Still, the measurements at this stage easily display a definite halt in the otherwise upward march of affairs, and they confirm the retardation which is clearly brought out in the curve itself. Such a course of events is quite naturally of considerable interest on both the dynamic as well as on the clinical side of the problem. It is not difficult from the former standpoint to understand why the curve should behave in such a peculiar fashion; nor is it easy, once this leveling stage is recognized, to avoid hazarding an interpretation as its clinical significance. Among other things,† it seems to touch fundamentally upon the extremely important and rather common complaint of childhood anorexia.

*One of the most fundamental distinctions arising in analytical work is exemplified here, for it may be noted that curves U and (Uz) have been obtained by applying our equations, as developed on independent grounds, to data on heat production rather than by attempting to deduce the trends directly from or out of the original set of observations. A similar remark applies to the weight curve z.

†The intriguing deflections in (Uz) and in U of Figs. 4 and 5 are, biologically speaking, the direct counterpart of similar postnatal, or even prenatal, events in other organisms, namely in the toad, chick, pigeon, rabbit, pig, guinea pig, and calf. These are superlatively set forth and interpreted in the monumental work of Needham.[44] Since then, additional data reported by Riddle, Nussmann and Benedict,[45] disclose similar phenomena in another race of pigeons. Exactly the same fundamental features are to be found in the curves for heat production among unicellular organisms exemplified in the painstaking work of Bayne-Jones and Rhees,[46] as well as in the later data by Schmidt.[47] The peaks and troughs of metabolism in all of these cases are generically related to the basic dynamic properties and events of growth, their connection with growth being most directly expressed by means of the equations we have elsewhere described.[1, 2] With this scheme of unification in mind opportunities for further work become almost boundless.

Physiologic Basis of Preschool Anorexia.—Consider for a moment the following course of reasoning. A healthy baby requires, on the whole, more and more food as it grows older and as it gains in weight. This general rule applies with greatest force, as we may infer, to the first year of life and to the period succeeding the age of five years. During the period between these ages there seems to be good reason that a mother, not necessarily an overzealous one, should seek an explanation of some kind when she finds a thriving, active, and healthy infant, fifteen months old, manifest no additional interest in food that does not remarkably exceed the quantity or differ much in kind from the habitual menu of the preceding 3 to 6 months. Having observed the definitely increasing quantities which the baby's appetite demanded during the first year, she is bound to expect further and regular additions now. Something more than solicitude is likely to develop, when she realizes that the day's supply at eighteen months, at 2 years, even at 2½, 3, and 4 years differs so insignificantly from that required during the previous stages of this epoch. Did not the one-year-old baby take a quart of milk vigorously, a volume that has gradually been reduced to two or three glasses a day? Have not the five meals of infancy been cut to four and then to three? The mush and vegetables remain the same, and the child, now fully a year or two beyond, lives literally on air! Small wonder that certain mothers should become unduly disturbed by this failure to eat and this obvious loss of appetite! As proof for their contention they are likewise apt to point out that the child has also failed, in comparison with the year before, to accomplish its expected gain.

Is it not perhaps deeply significant that this oft-repeated episode should fall precisely at the very period when basal heat production, as demonstrated by this curve, is oscillating with comparatively small amplitude about the 650 Cal./Day level and, as we have also seen, just at the time when growth and gain are likewise at their lower levels? For the frequency of anorexia, whether real or unreal, during early childhood is attested to in the experience of every pediatrician. On the basis of the present computations, as displayed in the foregoing curves, it seems altogether logical to conclude that a child's appetite is rather definitely, if not entirely, controlled by the basic physiologic mechanisms concerned with the fundamental processes of growth and metabolism. The striking fact is that heat production throughout this stage of life is at low tide, as is growth itself; and it seems unlikely, in consequence, that the call for food should be great when the basal rate of energy expenditure is so distinctly retarded and even slightly reversed.

Before leaving this question we should note that the values for heat production given in Figs. 4 and 5 do not refer to total daily energy requirements. The latter are obviously always greater than heat output, or no growth of any kind could be accomplished. An allowance of

about 1,000 to 1,500 Cal./Day, or between 400 and 750 Cal. in excess of "basal needs" is known[48] to be sufficient for the purpose of creating new cells, for storage, activity, and for other expenditure during preschool life.

To sum up, the basic events here emphasized are those in which we have seen a clearly defined halt in heat production, in the rate of gain, and in growth itself. We are inclined, therefore, to infer that the *physiologic* basis of preschool anorexia is to be found in a lesser demand for energy on the part of a healthy organism during the very years in which there is comparative "rest" in "the motion of growth."*

SUMMARY

Relying upon material embodied in preceding papers of this series as a guide we have here reviewed certain problems of human growth and metabolism which possess noteworthy clinical importance. The results apply chiefly to infancy and to preschool life, and they may be summarized as follows:

1. Matters of human growth are comprehended best when treated hand-in-hand with those of basal heat production. To this end individual attention has therefore been paid to careful definition and explanation of terms, more especially to "growth" and "gain" on the one side, and to "heat production" and "metabolism" on the other.

2. Growth cannot be properly understood by studying merely successive change in size. The latter is but one of many items equally important to the solution of any problem in this field.

3. Seven additional items are tabulated; these, acting in conjunction with the fundamental properties of growth resistance ρ, inductance λ, and permittance κ, we have previously defined, are dynamically responsible for the changes in size that result in cumulative gain. Together they characterize the various states of growth through which healthy subjects habitually pass.

4. Life trends of growth and rate of growth and the corresponding trends of basal heat production are compared with the more familiar curves of cumulative weight and rate of gain. The chief events are most conveniently grouped about the two major deflections (circumnatal and adolescent) in the rate of gain and in the pause between them. Normal full-term birth takes place at the moment when the rate of gain in weight has reached the highest peak of life. This maximum value in health is slightly less on the average than 1 ounce (27.8 gm.) per day. The rates of gain and growth both slow down remarkably during preschool life to reach their individual minima at 3.30 and 3.65 years respectively. Thereafter they rise to more widely separated maxima during adolescence.

*It is finally of interest that Plato had classified growth as the sixth in a group of ten kinds of motion.[49]

5. The production of heat to which the term "metabolism" most suitably refers is measured in *Cal./Kg./Day*, because it is held desirable, in dealing with subjects of varying age and hence of varying size, to make comparisons of heat output in relation both to size as well as to time. But the simpler unit, *Cal./Day*, is inherently subject, so long as growth persists, to the lesser relative error in respect of weight, though it suffers the theoretical defect of relating heat output solely to time, rather than to size as well as to time. When growth has ceased, the reverse is true.

6. One of the difficulties of rearing premature infants appears to exist in the stresses of growth which these subjects are required to withstand and to overcome under the comparatively adverse conditions of extrauterine existence. Such stresses arise during periods of natural acceleration in the rate of gain and they cannot be eliminated by external adjustments of any kind. They constitute additional risks which may be minimized by proper feeding and care.

7. From the dynamic point of view we regard the physiologic loss of weight at birth as an accidental and not as a fundamental event in the clinical careers of newborn infants.

8. Excessive rates of gain during infancy are followed by periods of delay in growth, such rates being accompanied by, and giving rise to, even greater rates of energy dissipation.

9. It appears unwise even in the face of the great individual differences so frequently witnessed in practice, to infringe upon the rule that no healthy infant requires to gain more than one ounce a day to assure its full attainment of growth.

10. Growth, gain, and basal heat production are all at low tide during preschool life. The year between three and four is most conspicuous in this respect.

11. The leveling-off of heat production between 1 and 4½ years seems to touch fundamentally upon the problem of preschool anorexia. We conclude that the *physiologic* basis of this oft-repeated event is to be found in a relatively low demand for energy on the part of a healthy organism during the very years in which we see comparative "rest" in the "motion of growth."

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SIMPLIFYING THE PROBLEM OF INFANTILE ECZEMA

An Analysis of 157 Cases

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THE classification of infantile eczema as a symptom of allergy has done much to simplify a difficult problem. It has also placed treatment on a more rational basis. While many cases are still baffling, especially those which have become chronic, knowledge of the more common etiologic factors makes the study less complicated.

FREQUENCY OF OCCURRENCE

In a previous paper[1] on eczema I reported a study of 989 children between the ages of one month and four years, with an incidence of 6 per cent.

IMPORTANCE OF FAMILY HISTORY OF ALLERGY

Of 157 cases studied, there was a positive family history of asthma, eczema, or some other symptom of allergy, in 109 cases, or 69 per cent. There was no history of allergy in thirty-nine cases or 25 per cent, and an unknown history in nine cases, or 6 per cent.

Balyeat[2] reports a positive family history of allergy in 76.6 per cent of a series of 181 cases of eczema.

O'Keefe and Rackemann[3] found only 28 per cent with positive family histories in their series of 212 cases.

Hill[4] is of the opinion that true hereditary transmission is relatively unimportant in eczema.

In the larger group of 220 cases I have seen, the incidence of allergy in the family history is well above 50 per cent and I believe that heredity is a strong predisposing factor in eczema.

DIFFERENTIAL DIAGNOSIS

There is a wide variety of skin diseases easily confused with eczema. Table I lists ten such diseases which were sent to the Central Presby-

Table I

Conditions Confused With Eczema

Seborrheic Dermatitis	12 cases
Impetigo Contagiosa	5 "
Napkin Dermatitis	5 "
Scabies	5 "
Ichthyosis	4 "
Mercurial Dermatitis	2 "
Ringworm	3 "
Paronychia	2 "
Pityriasis Rosea	1 "
Syphilis	1 "

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terian Clinic with diagnoses of infantile eczema. The table gives some idea of the relative importance in differential diagnosis.

ETIOLOGIC FACTORS

Scratch testing provides a simple, and in the very young, a reliable method of diagnosis of infantile eczema. The skin of infants reacts readily, though with widely varying degrees of intensity, to the application of powdered extracts. The reaction, in my experience, has much more frequently been an erythematous area around the scratch than a true wheal. Any reaction greater than the control should be regarded as important.

Common foods, as shown in Table II, are almost exclusively responsible for infantile eczema. If sensitization to unusual or occasional foods is present, the result is usually a transient urticaria rather than an eczema.

As the age of the child increases, the importance of foods as etiologic factors decreases and contact dermatitis, as described by Bloch,[5] Shelmire,[6] and others, assumes a place of much greater importance. It would seem that the eczemas of infancy and early childhood are largely of endogenous origin.

TABLE II

SHOWING FREQUENCY OF SKIN REACTIONS

Cow's milk alone	35 cases	Milk in combination	89 cases
Eggs alone	9 "	Eggs in combination	69 "
Cereals alone	0 "	Cereals in combination	53 "
Oranges alone	2 "	Oranges in combination	10 "
Tomatoes alone	1 "	Tomatoes in combination	6 "
Unusual foods alone	0 "	Unusual foods in combination	14 "
Causes undetermined		17 cases	

It is evident that milk is the greatest single causative factor in this series. In the thirty-five cases in which it was the only factor, 70 per cent of the patients were under six months of age. Milk sensitization would seem to occur very early, probably in utero.

Eggs alone accounted for only six cases. Of these 50 per cent were under six months of age and evidently had acquired sensitization through the mother. Eggs, in combination with other foods, were involved in sixty-nine cases.

Cereals alone did not account for any cases, but in combination were responsible in forty-nine cases. Forty-seven per cent of the cereal reactions were in infants between six and twelve months old.

Milk, eggs, and cereals accounted for 126 cases, or 80 per cent of those studied.

Table II brings out the very important fact that sensitizations are usually to more than one food. This explains the difficulties of diagnosis by diet elimination alone as described by Rowe,[7] Waters,[8] Dale and Thornburg,[9] and Hopkins et al.[10]

TREATMENT

Local treatment was avoided, excepting the use of white vaseline, so that whatever results were obtained could be properly evaluated. Offending foods were eliminated and, where necessary, substitutes were given.

Vaughan[11] and Ellis[12] emphasize the importance of group sensitization to foods having a common biologic origin. For instance, an infant sensitive to cow's milk is rarely able to use goat's milk as a substitute. Sensitivity to wheat frequently means sensitivity to other cereals such as oats and rice. Failure to recognize this fact causes many disappointments in treatment. Groups of common origin should certainly be eliminated in beginning treatment.

Slightly milk-sensitive infants often are able to tolerate a formula of evaporated milk heated to the boiling point for two or three hours. Soy bean milk has been the most satisfactory substitute where milk alone is responsible for the eczema. I have used it satisfactorily in twenty-nine out of thirty-two such cases. It contains a considerable quantity of cereals, and for that reason is often a failure as a substitute in infants who are sensitive to cereals as well as milk. Cohen et al.[13] have introduced a milk-, cereal-, and egg-free diet, which should fill an important need. From a practical standpoint it is too expensive to be widely used, and I have had difficulty because of its lack of palatability.

Every trace of the guilty foods should be removed from the diet for a period of two or three months. Frequently this is not done by the mother who fails to realize the frequency with which common foods, such as milk, eggs, and wheat, are used in preparing other foods.

Waters[8] calls attention to the ingredients of some of the common foods which frequently contain small amounts of the prohibited proteins. For instance, milk is contained in such foods as butter, cheese, ice cream, macaroni, margarine, white bread, puddings, cream soups, cakes, malted milk, milk chocolate, waffles, and pancakes. Eggs are found in mayonnaise, noodles, custards, milk puddings, rolls that are glazed with eggs, cakes or cookies, soft or filled candies, ice cream, hot breads, and chocolate preparations such as Ovaltine. Wheat is found in all breads, crackers, cakes and cookies, any foods using flour for thickening, malted milk, spaghetti, macaroni, noodles, breakfast cereals, rye bread, and oatmeal cookies.

After complete elimination for a time, it is usually possible to return to the guilty foods slowly, one by one, without trouble. Nature eventually takes care of most of the desensitization.

RESULTS

Table III shows the results obtained in this series of cases. The number of complete recoveries is high, perhaps too high, and probably would not hold for a larger series. Reasons for the favorable results are: that

77 per cent of the patients were under two years of age, that the skin of infants and young children is much more sensitive to testing and gives fewer false positive reactions, and that common foods are largely responsible in this age group. Contact sensitization, which occurs later, is not a factor of importance in infancy, and hence one of the chief complicating difficulties in diagnosis and treatment is removed. The fact that chronic eczema is seen infrequently in the very young helps to give a higher percentage of recoveries.

TABLE III

Complete recoveries	124—78.5 per cent
Improved	13— 8.0 per cent
Failures	20—13.5 per cent

CONCLUSIONS

1. Most true infantile eczemas are probably allergic in origin.

2. Milk is the most important single factor in the production of infantile eczema. Eggs are next in importance, and cereals complete the group of foods responsible for the majority of infantile eczemas.

3. Sensitization to more than one food is more common than sensitization to a single food.

4. Skin testing by the scratch method is both reliable and simple in the very young.

5. Sensitization to more than one food makes the diagnosis by diet elimination difficult.

6. Treatment by elimination of offending foods seems to be a logical plan. Soothing local treatment helps to increase the rapidity of recovery.

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205 EXCHANGE BUILDING

ACRODYNIA

(Erythredema, Polyneuritis, Vegetative Neurosis, Pink, or Swift Disease)

A Histopathologic Study of the Nervous System

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THE clinical aspects of acrodynia are well known and established. The etiology of the disease is still obscure. Infection, toxins and dietary deficiency have been considered as causative agents. The scanty and conflicting pathologic reports, especially of the nervous system, warrant a complete report of this case.

REPORT OF CASE

W. K., a boy, aged two years, suffered from loss of weight, anorexia, diarrhea, irritability and a rash. About the latter part of March, 1931, the patient fell twice from a height of about four feet, striking the back of his head. Following this, he began to refuse food, became irritable, and lost considerable weight. He would rock from side to side, forward and backward, until he fell on his back exhausted. On these occasions his penis was noticed to be erect. He would bang his head against the crib and would bite on his right big toe unless restrained. The stools became loose, bulky, and frequent. A rash first appeared on his face and later spread to the trunk. The soles of the feet and the palms of the hands became red, shiny, and peeled.

History.—The patient, a first child, was normally delivered at term, and weighed 6 pounds. He was breast fed for 4 months, but did not gain in weight. After he had been placed on an evaporated milk formula, cod liver oil and orange juice, his weight increased to 20 pounds at one year of age. For the next six months he received Imperial Granum and cow's milk, as well as cereals and vegetables. He continued to gain until the onset of the present illness when he weighed about 25 pounds. He sat up at 8 months, had his first teeth at about the same time, and walked at 13 months. He was exposed to tuberculosis in the paternal grandmother for a short time.

Examination.—The patient, first seen on June 23, 1931, was poorly nourished, irritable and tried to bite on his toes through the shoes. A few impetiginous lesions were present on the chest. A red, raw-looking, papuloulcerative rash covered the buttocks, scrotum, and anterior surface of the penis. The soles and palms were red and peeling. The cervical glands were slightly enlarged and firm. The pupils reacted to light and in accommodation, and the deep reflexes were normal. There was no evidence of rickets; the fontanels were closed. Eighteen sound teeth were present. The heart and lungs were negative. The liver and spleen were not palpable. The blood pressure was 90 systolic and 60 diastolic.

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Course.—The stools improved on ordinary protein milk. Any other addition to the diet, such as banana, orange juice, or cheese caused them to become loose. The patient continued to suck his hands and to bite anything he could get into his mouth. The arms and legs were splinted, but despite this the nails of the right big and middle toes were gone. Quartz lamp treatments were given twice a week. On August 6, 1931, his weight was reduced to 17 pounds.

On August 27 the rectum prolapsed with each bowel movement. The right and left big toes became ulcerated and the metatarsal bone of the right big toe was exposed. All the nails of the right foot, except that of the small toe, were gone. The inguinal glands were swollen. With the administration of atropine the soles and palms lost their redness, but continued to peel. The patient was admitted to the Barnert Hospital on September 4 and except for a few impetiginous lesions about the mouth and swelling of the feet, his condition remained unchanged. The blood pressure was 115 systolic and 75 diastolic.

Laboratory data.—Urinalysis was negative except for a positive urobilinogen test on one occasion and an occasional pus cell and red blood cell two other times. Examination of the blood revealed 3,750,000 red blood cells, 62 per cent hemoglobin, 16,800 white blood cells, 26 per cent lymphocytes, 2 per cent large mononuclears, 4 per cent eosinophils, and 68 per cent neutrophils. The blood Wassermann, Meinicke and Mantoux (1.0 mg.) tests were negative. A roentgenogram of the chest was normal. Stool examinations were negative for ova and parasites. It revealed abundant amounts of starch and fat but no neutral fat. Blood calcium was 10.2 mg. per cent and phosphorous 5 mg. per cent.

Course in the hospital.—The patient lost weight progressively. He sweated profusely about the head. When he was restrained, he lay quietly on his back; but as soon as the limbs were released, he would rub his hands and feet against each other or on the mattress. On September 9, the blood pressure was 126 systolic, and 70 diastolic. A direct blood transfusion was given the following week. During the first two weeks in the hospital, the temperature varied from 90° to 101°; during the last week it was subnormal. The extremities became cyanosed, and the patient died on September 26, 1931.

AUTOPSY

A necropsy was performed by Dr. H. Wassing soon after death. The body was extremely wasted. There was necrosis of the distal phalanx of the right big toe with involvement of the head of the metatarsal superficially. The skull presented no abnormalities. The thymus was small and weighed 3¼ grams. The liver was mottled and, on section, showed grossly grayish yellow areas alternating with hyperemic reddish brown areas. The spleen showed macroscopically no lymph follicles. The pancreas, adrenals, and the kidneys were normal. The entire large intestine and ileum disclosed marked atrophy of the mucosa and Peyer's patches. All the other organs were normal.

Microscopic examination of the internal organs was negative. A section of the skin of the palmar surface of the index finger stained with hematoxylin and eosin showed the usual increase in depth of the epidermis, mainly the result of the increase in the stratum corneum. There was no parakeratosis. The sweat ducts and glands were normal. The capillaries in the subpapillary zone were increased in number and slightly hypertrophied; these were lined with slightly hypertrophied endothelium. There was a moderate edema in the subpapillary and papillary zones surrounding the larger capillaries. The collagenous tissue seemed degenerated in areas and was edematous throughout. The elastic tissue could not be judged by this stain. The subcutaneous fat and the nerve fibers which could be identified were normal. The conspicuous features were: (1) dilatation of the capillaries of the papillary and

subpapillary zone with slight endothelial hypertrophy; and (2) moderate edema of the cutis with occasional focal areas of collagenous degeneration.

Nervous system.—(Gross examination.) The brain was cut horizontally. There was a slight discoloration of the putamen and caudate.

(Microscopic examination.) Sections from the various parts of the cortex, basal ganglia, pons, cerebellum, high cervical cord, and peripheral nerves were stained with the myelin sheath, cresyl violet, Bielschowsky, and Sudan IV methods.

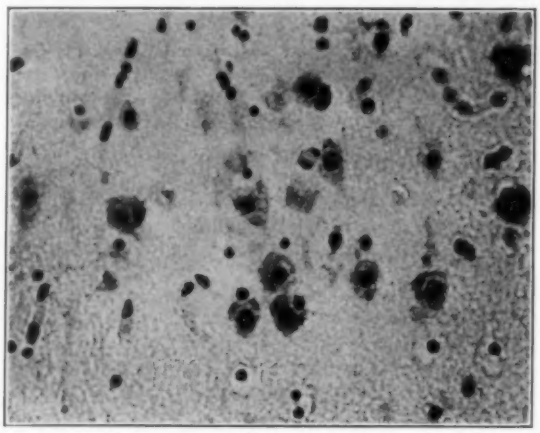

Fig. 1.—Nerve cells from the third cortical lamina showing swelling, loss in Nissl substance, and deeply stained nuclei. (Severe nerve cell disease of Nissl.) Cresyl violet stain. ×400.

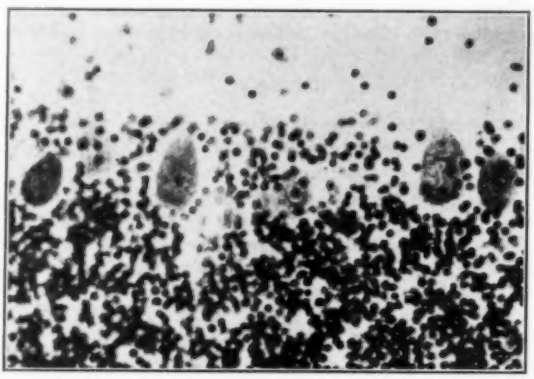

Fig. 2.—Swelling of the Purkinje cells, loss in chromatin material (homogeneity), and poorly stained cytoplasm and nucleus. Cresyl violet. ×400.

Brain: (Cortex.) There was a slight disarrangement of the cytoarchitectural layers. The ganglion cells of all the cortical laminae, mostly those of the third layer, were swollen; their outlines were indistinct and the Nissl substance stained poorly; the nuclei and nucleoli were deeply stained but were not displaced to the periphery (Fig. 1). Complete chromatolysis and falling out of single ganglion cells were also observed. There was a slight increase in the glia nuclei. The cortical

vessels were slightly engorged. Fatty granules and droplets were found in the ganglion and glia cells and in the walls of the blood vessels.

Basal ganglia: Horizontal sections of the brain through the island of Reil, including the putamen, caudate, and part of the thalamus, disclosed swelling of the ganglion cells of the neostriatum and thalamic nuclei; these nerve cells were not as extensively diseased as those in the cortex. The large ganglion cells of the striatum were more swollen than the small nerve cells. The nerve cells of the tuber cinereum appeared normal. The ependyma, except for a slight subependymal reaction, was normal. The ganglion cells of the cortical convolutions of the island of Reil showed the same changes as those described in the other cortical convolutions. Fatty deposits were also found in the nerve and glia cells and the walls of the blood vessels of all these structures.

Pons and cerebellum: There was insignificant paling of the corticobulbar fibers. The Purkinje cells of the cerebellum were swollen; they were poor in chromatin and their processes could not be visualized in the cresyl violet sections (Fig. 2). The glia cells were also swollen. In the Bielschowsky preparation a number of the

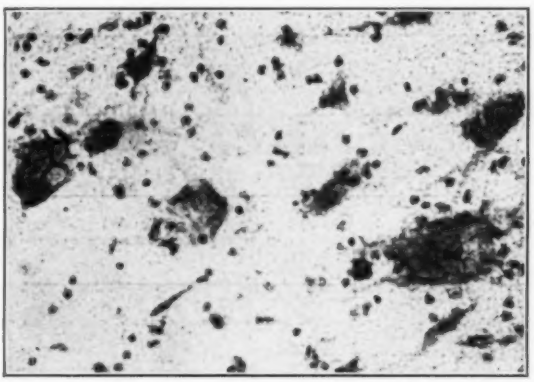

Fig. 3.—Severe cell changes of Nissl in the nerve cells of the locus ceruleus with decrease in pigment, vacuolization, and loss in outline of the cells. Cresyl violet stain. ×350.

Purkinje cells showed absence of the fibrillary processes; their axones and dendrites were swollen, and their fibrillae had disappeared. The nerve cells of the locus ceruleus were swollen, vacuolated, devoid of iron pigment, and showed the severe cell changes of Nissl (Fig. 3). The other ganglion cells about the fourth ventricle and the pons were also slightly swollen, but not quite as markedly as those of the locus ceruleus. The vessels were slightly engorged. The ependyma of the fourth ventricle was normal.

Spinal cord: Only a section from the high cervical region, in close proximity to the crossing of the pyramids, was obtained. The ventrolateral tracts took the myelin stain quite poorly (Fig. 4). With higher magnification, disintegration of single fibers was seen in the spinoolivary and dorsospinocerebellar and ventrospinocerebellar pathways (Fig. 5). The posterior columns were normal. The disintegration in the above tracts was mild in degree. The occasional disintegration of a single fiber of the lateral pyramidal tracts was also noticed. The motor cells of the nucleus ventralis of the eleventh nerve and of the anterior horn cells showed loss of Nissl substance and vacuolization (Fig. 6). Swelling as seen in the cortex

was not observed. Most of the changes were in the ventrolateral and ventromesial cell columns. The cervical cells of the nuclei of Stilling and of the substantia gelatinosa rolandi were normal.

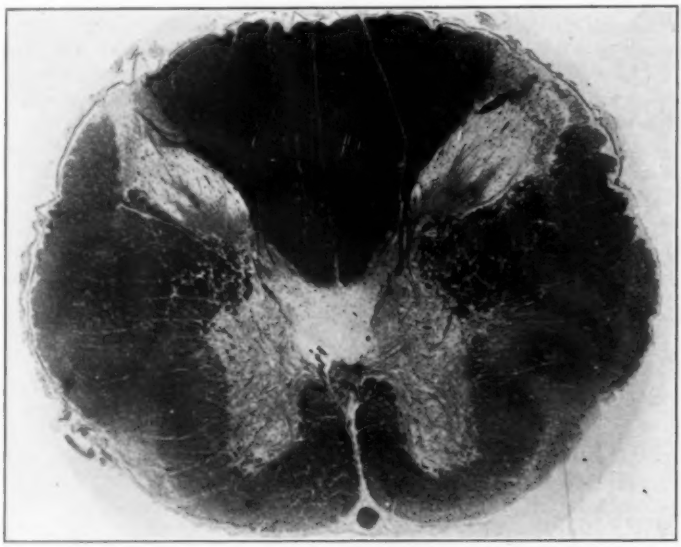

Fig. 4.—High cervical region showing marked poverty and paleness in the staining quality of the ventrolateral tracts. The posterior columns are intact. Myelin sheath stain.

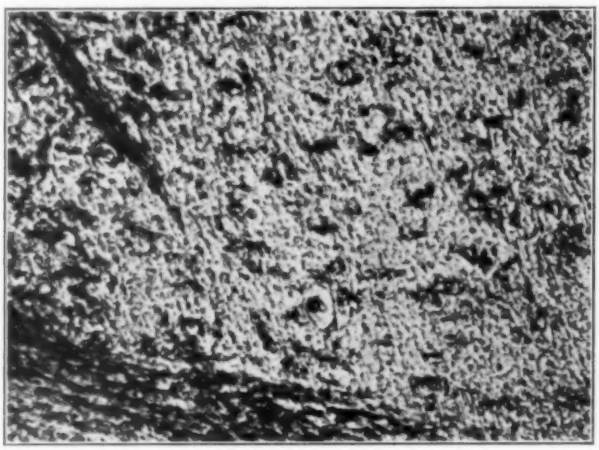

Fig. 5.—Disintegration of the myelin sheaths in the spinoolivary and cerebellar pathways. Myelin sheath stain. ×300.

Peripheral nerves: In the sections stained for myelin sheaths, there were areas of demyelinization throughout these nerves (Fig. 7). With higher powered magnification, early disintegration and swelling of the myelin was observed. The

process apparently was too early for marked formation of macrophages. In the Bielschowsky preparation there was breaking down of the axis cylinders; some were swollen and had ball-like terminations; others had a corkscrew appearance. The pathologic process was more advanced in the peripheral nerves of the lower extremities.

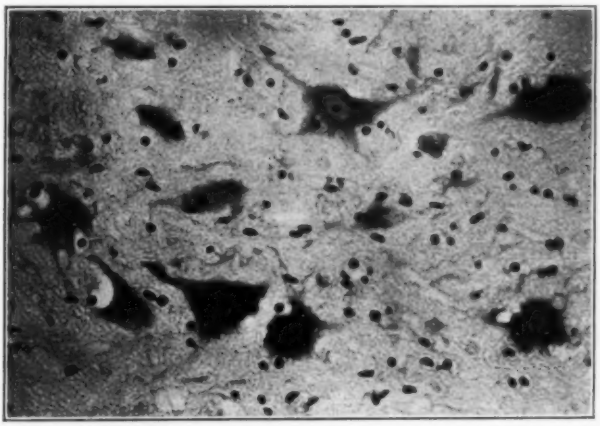

Fig. 6.—Vacuolization of anterior horn cells. Cresyl violet stain. ×350.

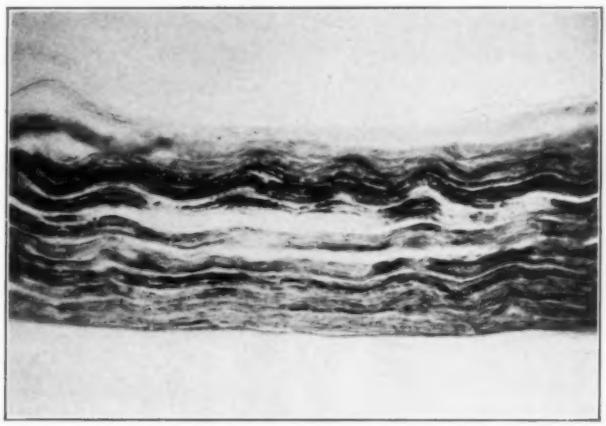

Fig. 7.—Demyelinization and distintegration of the myelin in the peripheral nerve. Myelin sheath stain. ×80.

SUMMARY OF CASE

Clinically, we are dealing with a typical case of acrodynia. Pathologically, the findings of the central nervous system are of great significance. These consisted of swelling of the ganglion cells of the various cortical areas, but mainly of the nerve cells of the third cortical lamina.

A similar process was also found in the large nerve cells of the neostriatum, the Purkinje cells of the cerebellum, and in the nerve cells of the locus ceruleus. The cells of the eleventh nerve nucleus and of the spinal cord were vacuolated. There was slight demyelinization of the ventrolateral tracts of the spinal cord and marked demyelinization of the peripheral nerves, especially those supplying the lower extremities.

COMMENT

The vasomotor and trophic disturbances in acrodynia have led some observers to believe that it is a disease of the vegetative nervous system with involvement of the sympathetic fibers of the peripheral nerves, the sympathetic cells (lateral column cells) in the spinal cord, and the diencephalic and mesencephalic vegetative centers. The alterations in the central nervous system of our case justify an analysis of the neural changes described by others.

Peripheral nerves.—Patterson and Greenfield[1] described in Case 1 a certain amount of long standing degeneration of the musculocutaneous nerve; in their Case 3 the internal and external popliteal nerves showed considerable evidence of myelin degeneration, and the finer nerve bundles in the muscles were also demyelinated. Kernohan and Kennedy[2] reported an involvement of all the peripheral nerves, especially the sciatic and femoral. Changes were also found in the peripheral nerves of Wyllie's and Stern's series[3] in four out of seven cases; not the same nerves were involved in all cases.

Spinal cord.—Byfeld[4] reported occasional anterior horn cell involvement. Patterson and Greenfield[1] described chromatolysis and vacuolization of the motor nerve cells of the cord. Wyllie and Stern[3] observed similar changes in five out of their seven cases. Kernohan and Kennedy[2] found chromatolytic changes in the sacral anterior horn cells and considered these as axonal degenerative reactions. Orton and Bender[5] described loss of nerve cells and nerve fibers and fibrous glia replacement in the lateral horns of the thoracic and lumbar regions. Some of the above authors also described infiltrations of the cord with glia cells. (Patterson and Greenfield[1] and Wyllie and Stern.[3])

Cortical and subcortical centers.—Cornelia de Lange[6] found diffuse glial increase in the tuberoinfundibular region and a moderate glial increase in the lenticular nucleus, anterior nucleus of the thalamus, and dentate nucleus. Kernohan and Kennedy[2] were the first to report chromatolytic changes in the nerve cells of the basal ganglia, midbrain, medulla oblongata, gasserian ganglia, and dorsal root and mesencephalic root of the fifth nerve. The nerve cells of the locus ceruleus were particularly involved. They did not study the vasomotor and sympathetic systems.

Other observers did not find any changes in the nervous system. Warthin[7] only found edema of the meninges. He believed that the degenerative changes in the peripheral nerves and the chromatolysis of nerve cells in the brain and cord are postmortem in character. Wyllie and Stern[3] also believed that the changes described by Kernohan and Kennedy[2] were not abnormal in the situations mentioned, but the latter, however, insisted that there were definite changes in the mesencephalic root of the fifth nerve and also in the ganglion cells of the thalamus.

The findings in our case are somewhat similar to those described by Kernohan and Kennedy.[2] Unfortunately, in our case the gasserian ganglion and the thoracic and lumbar segments of the spinal cord, were not secured at autopsy.

Undoubtedly some of the neural changes in acrodynia, such as the vacuolated cells of the spinal cord and the swollen and chromatolytic cortical and Purkinje cells, may be attributed to the extreme state of starvation or exhaustion. Whether these induced the severe cell alterations of Nissl observed in the nerve cells of the locus ceruleus cannot be answered satisfactorily. The peripheral nerve degenerations can also partially be explained on the above basis. One of us, Davison,[8] found such changes in some animals which were completely deprived of food. It is also worth mentioning that in the experimental animals, priapism, as noticed in our patient, was not an uncommon finding. As the patient took nourishment poorly, the question of exhaustion or starvation should be considered as a causative factor in the pathology of the central nervous system.

The etiology of this obscure disease has not been solved as yet. Patterson and Greenfield[1] think that the polyneuritis is caused by the toxins of some microorganism, and not by a metabolic disorder as is postulated in beriberi or pellagra. Acrodynia appears to have occurred more frequently during and after epidemics of influenza, and it is usually preceded by an influenzal cold. Byfeld[4] suggested that the polyneuritis in acrodynia is a form of diphtheric neuritis for he found diphtheroid organisms in the nasal secretion of his cases. He found that the lesion came on shortly after a severe cold and that its course was sometimes considerably shortened by the eradication of septic foci, as the tonsils. Warthin[7] thought that the picture resembled that of pellagra and on this basis he considered acrodynia as a deficiency disease. Wechsler[9] and others believe that some cases of obscure peripheral neuritis are not due to toxins or infection, but are the end-result of starvation, dietary deficiency—avitaminosis. The similarity of the histopathologic findings in the central nervous system of our case with those found in the dietary deficiencies and starvation would seem to suggest that the latter plays an important rôle.

CONCLUSION

A case of acrodynia is reported in a child of two years who presented the typical trophoneural changes observed in this disease. Histopathologic study of the nervous system revealed a marked swelling of the ganglion cells of the third cortical lamina, the large ganglion cells of the neostriatum, the Purkinje cells of the cerebellum and severe pathologic changes in the nerve cells of the locus ceruleus. In the cervical region of the spinal cord, there was some disintegration of the fibers in the ventrolateral tracts and loss of Nissl substance and vacuolization in the motor cells of the nucleus ventralis of the eleventh nerve, and in the ventrolateral and ventromesial anterior horn cells. The peripheral nerve changes were similar to those seen in peripheral neuritis.

A review of the neural findings in the cases recorded in the literature are too contradictory, and therefore, cannot be accepted as final. Little evidence has been advanced so far to establish the etiology of the disease.

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RICE POLISHINGS AS A SOURCE OF VITAMIN B COMPLEX IN INFANT FEEDING

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THIS study was undertaken to determine the beneficial effects, if any, in infants fed routinely with a food reinforced with rice polish as a source of vitamin B in its complex form.

Vitamin B, once considered a single substance, has been definitely demonstrated to consist of at least two distinct elements, a thermolabile, antineuritic vitamin B, or B_1 and a thermostable antidermatitic vitamin G, or B_2.[1, 2]

Recent investigations have indicated the possible existence of many more factors in this complex vitamin, thus raising the question whether or not some of the properties attributed either to vitamin B or G may not be due to other components, as yet, not clearly demonstrated.

According to Kruse and McCollum[3] "sufficient evidence has been adduced to indicate that the physiologic and pathologic effects ascribed to the antineuritic vitamin, at least in growth experiments on rats, are in reality the resultant of a multiple deficiency and are subject to revision as the nature of the B complex is amplified."

If, as Cowgill[4] feels, a subclinical deficiency of this vitamin exists in this country, then the clinical value of vitamin B is such that it far outweighs, and should not await, the scientific discussions and demonstrations of its various factors.

No attempt will be made here to assign any of the conclusions to any one factor, or group of factors, but rather to the whole vitamin as it exists in its complex form. Thus by the term vitamin B will be meant "vitamin B complex."

Experimentally it has been demonstrated that vitamin B promotes growth per se and by stimulating the appetite.[5]

The effects of a complete deficiency of this vitamin are well known clinically, whereas a partial deficiency has produced, according to Hoobler,[6] a symptom complex consisting of anorexia, loss of weight, spasticity of extremities, neck rigidity, restlessness, and fretfulness, together with pallor and low percentage of hemoglobin. Anorexia is the outstanding symptom of a vitamin B deficient diet in animals,[7, 8] and their food consumption was found to be dependent on the amount of this vitamin in the diet.[9]

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Dried milk used in this experiment was supplied by the Dry Milk Company.

Anorexia is a common complaint of infancy and childhood, and while it is not always attributable to a vitamin B deficiency, nevertheless, the addition of this vitamin has produced excellent results both in the normal[10] and the marasmic type of infant.[11, 12, 13] Dennett[10] secured good results in infant feeding by the use of a sugar rich in vitamin B and concurred with Hoobler[6] and Bartlett[14] in attributing anorexia in certain infants to a deficiency of this vitamin. Morgan and Barry[15] describe the beneficial effects of this vitamin both in weight and height increases on malnourished school children, while Summerfeldt[16] obtained similar results on a series of normal children. In view of this, one questions whether the average infant and child is receiving an amount of vitamin B sufficient to produce optimum growth. Sure[17] states that the requirements of vitamin B are greater in the growing young rat, while Supplee[18] and others have shown the growth response in rats to the water-soluble milk vitamin concentrate to be greatly enhanced by the addition of vitamin B as found in rice polish.

While cow's milk in one form or another is the main constituent of the artificially fed infant's diet, many investigators have found not only cow's milk, but also human milk, to be low in this vitamin, especially the antineuritic element.[19, 20, 21, 22, 23]

With this in mind it was thought desirable to note the effect on normal infants, artificially fed with a milk reinforced with vitamin B in the form of rice polish. In considering a substance rich in vitamin B to be added to an infant's food, care must be taken to see that the substance is such that it does not change the character of the food to which it is added, that it has no disadvantageous effects on the infant taking such food, and that the vitamin B consumption increases parallel to food intake and increase in weight.[24] Dennett[10] in using wheat-germ sugar as a source of vitamin B found it to be more laxative than other malt sugars, and occasionally so laxative that it necessitated the use of minimal amounts. While yeast may act as a proper supplement in older children, its potency varies considerably, and it is practically impossible to incorporate it in milk without affecting the taste of the milk and at times causing gastrointestinal disturbances.

Rice polishings, which are rich in vitamin B, especially the antineuritic factor, consist of the bran and germ of the rice kernel.

It is possible to prepare and compound with milk, a suitable water extract of rich polishings in a manner which does not affect the taste or keeping qualities of the milk. Furthermore, by employing the active constituents of the rice polishings in this manner, the vitamin B consumption increases parallel to the food intake.

The food used in this series of cases was a 2 per cent fat, irradiated, dried milk, to which was added a water extract of crude rice polish. A suitable method for preparing the water extract with a minimum amount of inert material and with a high vitamin B potency was pre-

viously determined by extended experimentation, involving the use of white rats as test animals.

Chart 1 was compiled from the average of several groups of experimental animals showing the resulting effect on growth of white rats, obtained when the regular dry milk was not fortified with rice polish, in contrast with results obtained when rice polish extracts were incorporated with the milk. The results shown by the "check group" were obtained when dried milk not fortified with rice polish constituted 10 per cent of the experimental ration, and wherein the milk served as the sole source of all the water soluble vitamins. Groups A, B, and C are similar averages wherein 10 per cent of dried milk, fortified with rice polish extracts in small but variable amounts, is included in the basal ration as the sole source of all the water soluble vitamins. These comparative results on experimental animals clearly indicate the improved nutritive

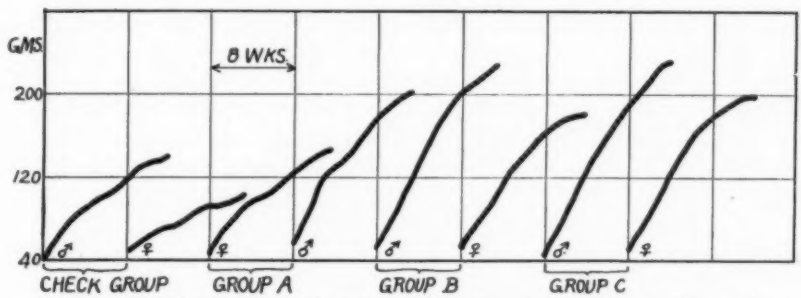

Chart 1.—Weight increase in rats fed dry milk with and without rice polish supplements.

quality of the milk fortified with vitamin B in the form of rice polish as contrasted with the same milk unfortified with rice polish.

The water extract of crude rice polish is simply made by agitating four parts by weight of water and one part by weight of crude rice polish at a low temperature for a few hours. The resulting infusion then should be freed from excess solids. The solid matter in the final extract has varied from 3.8 per cent to 4.9 per cent. This extract has been added to the 2 per cent fat, irradiated liquid milk and then dried by the roller process. The rice polish solids, as carried by the extract, have been in the neighborhood of 3.5 to 4 per cent of the total dry mixture. Thus 100 c.c. of the reconstituted, vitamin-B-fortified, dried milk contains 50 vitamin B units according to Sherman specifications, while 100 c.c. of reconstituted dried milk, not fortified, contains only 25 vitamin B units.

STUDY OF INFANTS

During the past year, one hundred normal infants ranging from newborn to six weeks of age were fed this 2 per cent fat, irradiated dried

milk, fortified with vitamin B as found in rice polish. No carbohydrates were added to the formula.

They subsisted on this milk for an average period of five months. As controls, without the addition of vitamin B, fifty normal infants were fed the same type of dry milk unfortified; thirty normal infants were fed various modified commercial evaporated milks; and twenty normal infants were placed on modified cow's milk formulas.

The dried milk fortified with rice polish was extremely well borne by these infants. For the first week or two, in some cases, the stools were more frequent and rather loose in character, but this quickly sub-

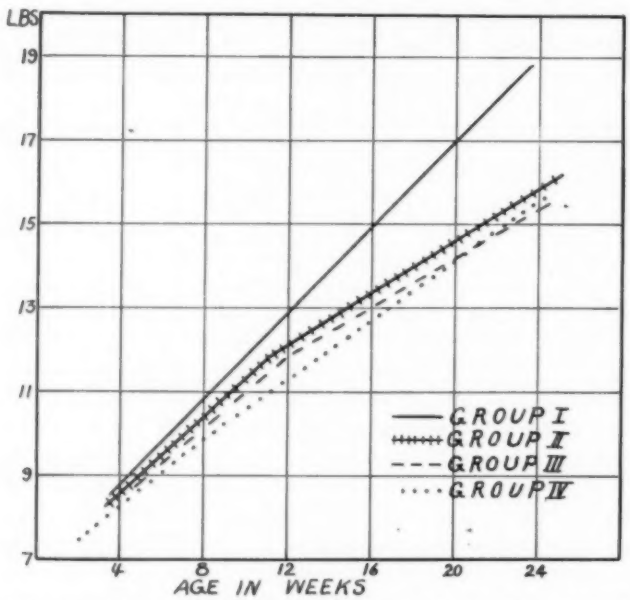

Chart 2.—Comparison of the increase in weight of infants. Group I, one hundred infants fed 2 per cent fat, irradiated dry milk fortified with a water extract of rice polish; Group II, fifty infants fed 2 per cent fat, irradiated dry milk not fortified with rice polish; Group III, thirty infants fed various modified commercial evaporated milks; Group IV, twenty infants fed modified cow's milk mixtures.

sided without affecting the appetite or gain in weight. From then on, no intestinal disturbances were noted, there being two to three formed stools a day. Constipation was entirely absent in these infants, and on no occasion was catharsis employed.

Chart 2 illustrates the average age in weeks in which the observations were started, the duration, and the gain of weight of these infants.

The great increase in weight of the vitamin B group substantiates Summerfeldt's[16] results with older children. While weight in itself may be a poor standard for determining the effectiveness of vitamin B

in infants, there being many methods of making a child gain, still it is a practical method of recording an infant's well-being.

Especially is this true when the weight of the vitamin B group is compared to the group of infants fed the same type of milk without the rice polish. That this increase in weight is not due to an increased caloric intake is demonstrated by the fact that the average daily caloric intake per pound per body weight in the vitamin B group was thirty-five as compared with from forty-five to fifty-five in the other groups. Thus in the vitamin B group, there was a greater metabolic efficiency which can only be attributed to an increased intake of vitamin B. No attempt was made to increase the gain in weight by forced feeding, nor were the old standards of caloric requirements adhered to in making up the daily formula. The daily intake of food was increased only when the infant was apparently hungry and showed his willingness to consume more.

Anorexia was entirely lacking in this group, as compared to the other groups in which there were six cases developing about the third month. Muscle tone was better and flesh firmer. The infants were restful, slept better, were mentally more alert, and less irritable than is usual. The common colics of infants were absent.

While these observations occurred during the fall and winter months when infants in this climate have less outdoor life, pallor was much less marked in this group. Skin and mucous membranes were free from lesions; there were two cases of eczema and four stomatitis in the other groups. Their physical development was more rapid as evidenced by earlier teething, creeping, and walking. Infections were much less common in this group, there being but one case of upper respiratory infection and one of pyelitis. In the other groups there were seven cases of upper respiratory infections complicated in two instances by otitis media, two cases of parenteral diarrhea, and one case of pyelitis.

Clinical evidence of rickets was absent in all the infants, the irradiated milk acting as the sole antirachitic when fed; the other groups received cod liver oil or viosterol in sufficient dosage.

When cereals and other foods were added to the diet, half of the experimental group was continued on the dried milk, fortified with rice polish, while the other half was given plain cow's milk. Over a two-month period those on the fortified milk made an average monthly gain of thirty-two ounces as compared to an average monthly gain of eighteen ounces of the group receiving cow's milk. Thus, the weight curve is immediately affected by the lowering of the vitamin B content of the food.

Chart 3 illustrates the weight curve of newborn twins fed at various intervals, fortified dried milk, and dried milk not fortified with vitamin B. It indicates the possibility that vitamin B influences the weight curve favorably, and furthermore, that infants have a low capacity for

tissue storage of vitamin reserve, as indicated by a comparison of the gain in weight of the two cereal groups.

Twenty-five abnormal infants subsisted solely on this 2 per cent irradiated dry milk fortified with vitamin B in the form of rice polish. In this abnormal group were placed infants with organic defects and disturbed digestive systems caused by inherent weakness and dietary abuses.

This group included premature infants and infants with mongolism, cretinism, cleft palate, harelip, pyloric stenosis, and pylorospasm. The

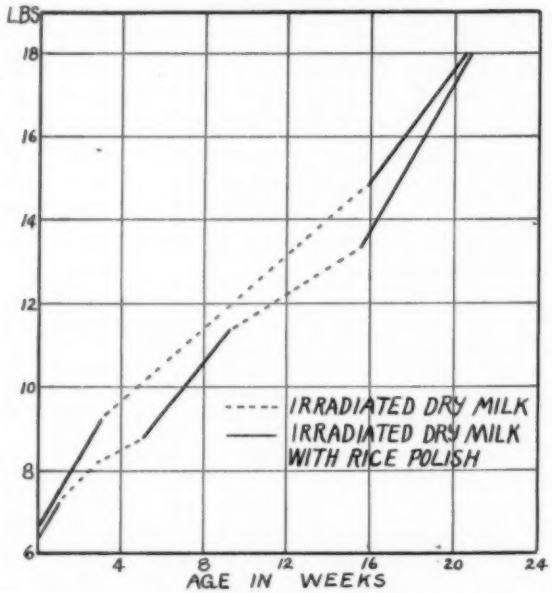

Chart 3.—Weight increase of twin infants fed 2 per cent fat, irradiated dry milk fortified and unfortified with a water extract of rice polish.

average gain in weight for the whole group was five and one-half ounces per week over a six-month period. Ten patients were operated upon, five for pyloric stenosis and five for harelip and cleft palate, without any untoward incidence and with unusual maintenance of nutrition.

Vomiting in nine cases classed as pylorospasm subsided rapidly without medication. One infant, six weeks old, presenting symptoms—similiar to a deficiency of vitamin B according to Hoobler, namely, spastic extremities, neck rigidity, weak cry, loss of weight, and anorexia—was placed on the fortified dried milk. Complete alleviation of symptoms occurred in three days, the appetite was markedly improved with resultant gain in weight and loss of spasticity.

SUMMARY

One hundred normal infants were fed a dried milk reinforced with a specially prepared water extract of rice polish as a source of vitamin B for an average period of five months. The increase in weight was influenced favorably; metabolic efficiency was increased; anorexia and gastrointestinal disturbances were lacking; pallor was less marked; and nutrition was improved and a greater resistance to infection exhibited. They were, as a group, mentally more alert and less irritable, sleeping better and possessing practically none of the common complaints of infancy, as abdominal colic, constipation, and excessive crying. Infants do not seem capable of storing vitamin B for future use.

CONCLUSION

1. The supplementing of cow's milk with vitamin B is desirable for optimum growth in infants artificially fed.

2. Rice polishings provide a good source of vitamin B for this purpose.

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ACUTE MENINGITIS DUE TO *BACILLUS FECALIS ALCALIGENES*

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THIS gram-negative organism, *Bacillus fecalis alcaligenes*, recognized first in 1889 has been considered a nonpathogenic organism and has been described as a normal saprophyte in man, having been isolated from blood, stools, and urine of healthy and sick individuals. However, the virulence of this bacillus may in certain cases be increased to such an extent that it becomes a real pathogen capable of producing definite systemic illness. Morbidity resulting from general infections caused by *Bacillus fecalis alcaligenes* is undoubtedly quite low, judging from the scanty literature on the subject.

In those patients with general infections caused by this specific organism the majority have had symptoms resembling typhoid fever,[1, 7, 8] with an associated bacteremia.[2, 3] The only pathologic report from this type of case is presented by Ravenel[4] who describes lesions in the lower ileum and large colon, which appeared to be typical early typhoid ulcers. This patient, a white male, twenty-one years old, died on the sixth day of illness. The spleen and mesenteric glands were grossly enlarged and cultures from the spleen and intestinal ulcers showed *Bacillus fecalis alcaligenes*. Recently an epidemic of conjunctivitis[5] occurred on board a British Naval Training ship and the causative organism when isolated was this same gram-negative bacillus. No systemic symptoms were reported.

The first case of meningitis caused by this organism was recently described by Gatewood.[6] The patient, a white male child with Jacksonian epilepsy, had a decompression operation, which was followed by symptoms of meningitis. The invading organism proved to be *Bacillus fecalis alcaligenes*, and the meningeal symptoms were relieved by adequate drainage through lumbar puncture. Convalescence was uneventful.

Another patient with acute meningitis in which the invading organism was *Bacillus fecalis alcaligenes* is herewith described.

H. M., a white adolescent female, twelve years old, was first seen October 25, 1930, with a complaint of pain in the lumbosacral region of two days' duration. Her past history was essentially negative. Positive findings on physical examination revealed a healthy adolescent female with a meningocele 6 cm. in diameter in the

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lumbosacral region, slight atrophy of the right thigh and leg, with pes cavus of the right foot. Roentgenograms showed a spina bifida occulta involving the upper segment of the sacrum and the third, fourth, and fifth lumbar vertebrae with a beginning spondylolisthesis of the fifth lumbar vertebrae.

Two days later the patient had definite signs of meningitis. She was hospitalized for a month and during the first two weeks had a stormy illness, associated with severe headache, backache, and acute, deep muscular pains in the thighs. There were periods of delirium, restlessness, and marked irritability. The temperature varied from normal to 102° F. The leucocyte count varied from 8,000 to 14,000 with a predominance of neutrophiles. The chief therapy, aside from symptomatic treatment, consisted of adequate drainage of the cerebrospinal fluid through cisterna puncture, twelve such punctures being made during the course of the illness.

The convalescence was uneventful. The child was carefully examined at one week, five weeks, four months, seven months, and twenty months following her discharge from the hospital. At first there was a slight residual papilledema of the optic nerve head, but this completely cleared; at the time of her last examination in June, 1932, there were no symptoms referable to her acute meningitis.

The laboratory data follow:

CISTERN FLUID

DATE	AMOUNT	CELLS	PANDY	PROTEIN (MG./100 C.C.)	SUGAR (MG./100 C.C.)	CULTURE	LANGE	MASTIC
10/27/30	50 c.c.	120	+	70	68	Neg.	0000223100	3322111000
10/28	60 c.c.	570	+			BFA		
10/29	60 c.c.	590	+	60	63	BFA		
10/30	60 c.c.	2,261	+			BFA		
11/ 1	60 c.c.	520	+	45	63	Neg.	0000112110	2222110000
11/ 2	50 c.c.	800	+			BFA		
11/ 3	60 c.c.	670	+			Neg.		
11/ 5	40 c.c.	420	+			Neg.	0011233100	3444432100
11/ 7	40 c.c.	220	+			Neg.		
11/10	30 c.c.	161	+			Neg.		
11/19	45 c.c.	40	−	10	10	Neg.	1111121000	1100000000
12/ 8	35 c.c	20	−	10	62	Neg.	0000000000	0000000300

Blood culture, negative.
Stool culture showed no growth of typhoid-dysentery group of organisms.
Urine culture showed *Staphylococcus albus.*
Blood and spinal fluid Kolmer and Kahn negative.
Widal, negative.
Blood serum showed no agglutination with *Bacillus typhosus; Bacillus paratyphosus A; Bacillus paratyphosus B;* or *Bacillus abortus.*
Blood serum showed no agglutination with organism isolated in pure culture from cistern fluid.
Agglutination with Flexner dysentery organism in dilution 1:160.
No agglutination with Shiga or Hiss Y organisms.

The organism isolated in pure culture from the cerebrospinal fluid of this acutely ill patient was a gram-negative, motile bacillus, producing no acid or gas in dextrose, galactose, levulose, lactose, mannite, or maltose. Indol formation was negative. Litmus milk turned alkaline. There was no liquefaction of gelatin.

COMMENT

In classifying the bacteria of the human intestine, Monias[9] describes a variety of different strains of this organism collected from various investigators, the essential cultural characteristics of which are described above. Evans[7] recently listed a new subspecies "radicans" which varies only slightly from the organism observed here.

The serology also varies according to various investigators, thus Wyatt[3] and Rochaix and Blanchard[8] observed that their patients' serum agglutinated the isolated organism; while in Evans'[7] patients, as in the one here presented, the organism was not agglutinated by the respective patient's serum. However, there seems to be a uniformity in all the reports as to the negative agglutination with *Bacillus typhosus, Bacillus Paratyphosus A,* and *Bacillus Paratyphosus B.*

One clinical feature which was observed by Shearman and Moorehead[1] and by Wyatt[3] was the marked pain in the lower extremities. Although the patients described by these writers had a generalized systemic illness, whereas our patient had a definite meningitis, there was, nevertheless, this same marked severe pain in the lower extremities.

SUMMARY

A case of acute meningitis caused by *Bacillus fecalis alcaligenes* is presented, in which a complete recovery was effected by adequate drainage of cerebrospinal fluid through cistern puncture.

The source of the infection could not be found either in the blood, stools, or urine of the patient, and it must be assumed that the causative organism gained access to the cerebrospinal system through a spontaneous opening in the meningocele.

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NEUROCYTOMA OF THE ADRENAL GLAND WITH METASTASIS

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TUMORS of the medullary portion of the adrenal gland are uncommon but are not rare. In a résumé of cases to 1917, Lehman[1] reported twenty-five cases, and made the statement that many more were probably reported as lymphosarcoma and round cell sarcoma. Since then forty cases have been reported, making, with this case, seventy-six in all.

The classification and identification of this group of tumors has been rather confusing as a result of the undifferentiated grouping of the cells. They have been called neuroblastoma, neurocytoma, paraganglioma, and lymphosarcoma. Pathologists are not in agreement as to the exact classification.

The reported cases have usually occurred in children under six years of age, and many of them in children under three years. The symptom-complex usually lasts about three months. The onset is usually insidious, but may be acute, beginning with loss of weight, diarrhea, vomiting, slight rise in temperature, ecchymosis over the eyelids, palpable mass in the abdomen, trauma over the site of the tumor, and various metastatic syndromes. The course is progressively downhill with a rapidly increasing anemia.

The gross pathology is distributed over the lympathic area which drains the adrenal involved. The so-called Hutchinson's tumor, with its predominance of metastasis to the long bones, skull, brain, and scalp, arises from the left adrenal in the majority of cases, but may arise from the right as in the case reported here. The Pepper type usually arises from the right adrenal and metastasizes to the liver, lung, and pleura. Ewing[2] gives the anatomy involved in the metastatic process. The tumors may vary in size from a walnut to a small cabbage; they are usually encapsulated. The color of the tumors is usually a pearly white, but they may shade from red to a brownish color. Areas of cystic degeneration are seen throughout the entire mass. The tumor lies free in the peritoneal cavity and does not metastasize by direct extension.

CASE REPORT

W. K., a three-year-old boy of German descent, was brought to the out-patient department of the Jefferson Davis Hospital June 7, 1933, at which time there was pain with swelling on the left side of his face, and some fever. On July 8, he returned to the emergency room where a fluctuant mass was opened. The mass

was located over the left mandibular ridge. Following the incision a small amount of pus exuded from the wound. He was referred to the ward on July 13 with a provisional diagnosis of osteomyelitis of the left mandible.

The mother stated that she noticed a small red pimple on the left cheek on June 24 and that about three days later she noticed some swelling of the left jaw. The jaw had continued to enlarge but had not been very painful except when the child opened his mouth. He had been unable to open his mouth for the past week. About two weeks before the swelling on the cheek was noticed the child complained of pain in the left shoulder.

Family History.—Negative for chronic, familial, or hereditary diseases.

Past History.—The baby was full term; delivery was normal. There were no convulsions, cyanosis, or paralysis noted. He was breast fed for the first three months, then bottle fed. The diet was prescribed by the mother. The child had always been a precocious eater.

Physical Examination.—On admission to the ward, the examination revealed a poorly nourished, yellowish, pasty, toxic white male lying quietly in bed. Over the mesial portion of the left frontal bone was a bluish tumor, slightly painful on palpation. It was firm and connected with the periosteum. There was a slight proptosis of both eyes. The lid of the left eye showed ecchymosis. The mouth showed a necrotic mass, with a foul odor and a serosanguineous discharge, attached to the left cheek, and extending from the angle of the mandible to the second molar. It seemed to be attached to the mandible and to the mucous membrane of the cheek. Pain was produced when the patient opened his mouth. The left side of the face showed a large swelling, which was not painful. The mass was white and shiny, and the superficial veins were dilatate. The tumor extended from the outer canthus of the left eye to the fourth cervical vertebrae. It could not be separated from the mandible. The salivary glands could be easily identified. The left posterior and anterior cervical glands were enlarged. A systolic murmur was present over the left second, right second, and left fifth interspaces. The murmur, not transmitted, had a soft blowing quality. The heart extended from the second interspace superiorly to the fourth interspace on the left side 8 cm. from the left border of the sternum. The right border was continuous with that border of the sternum. The abdomen was prominent with distended veins. The liver was palpable, soft, and smooth. It extended four fingerbreadths below the costal margin. The extremities were emaciated but not atrophic. The blood counts revealed a progressive anemia, which did not respond to any of the methods of treatment used. The urinalysis on several occasions showed mucous and hyaline casts. A blood culture taken on two different occasions showed no growth at the end of six days. The Wassermann and Mantoux tests were negative. The reticulocyte count was steadily increasing up to the time of death. Smears from the mouth taken on admission revealed Vincent's spirilla and fusiform bacilli. The blood chemistry was: nonprotein nitrogen, 62.15; urea, 30; sugar, 133.33; and creatinin, 1. Two weeks later the blood chemistry was: nonprotein nitrogen, 27.5; urea, 12.5; sugar, 103.2; and creatinin, 1.3. The x-ray reports are grouped at the end.

A diagnosis of neurocytoma of the adrenal gland with metastasis was made on July 14. The tumor mass increased steadily in size. On July 26, a mass was palpable in the right renal region. The tumor was incised the same day and the necrotic tissue removed. At this time it was considered an osteomyelitis of the left mandible. On August 1, the tumor over the frontal area was opened and a reddish piece of tissue removed. The surgeon considered this as a metastasis from an osteomyelitis of the left mandible. On August 12, the patient developed semicoma with the Jacksonian type of convulsions of the left side. This was relieved by glucose. The patient died, August 17, in a state of semicoma and convulsions.

Abstract of Autopsy (Dr. Harry E. Braun).—The body was that of a poorly nourished, well-developed white male. The skin was pale and pasty. A mass was present over the left mandible, left frontal bone near the midline, right parietal bone, and superior to the globe of both orbits. The mass over the left mandible and left frontal areas revealed old operative wounds.

The abdomen revealed a large tumor in the right renal area. It was cystic, maroon in color, and soft. It was not attached to the kidney, but began in the region of the right adrenal gland. The mass extended across the abdomen and was 20 cm. long and 6 cm. in breadth. There was no metastasis to any other organs of the abdominal cavity. The glands of the iliac region were enlarged. The thorax revealed a tumor in the sixth and seventh ribs on the left side. It was maroon in color and soft. A mass extending from the left side of the sixth cervical vertebrae to the second thoracic vertebrae was also found. All of the axillary, inguinal, cervical, iliac, and the right popliteal glands were enlarged. All enlarged glands and metastatic growths revealed the same type of tumors grossly. All of the long bones revealed pathologic fractures at the superior epiphysis, and the same type of tumor was found grossly. These metastatic tumors were growing in the marrow and had produced a great deal of de-

Fig. 1.—Cyst of left mandible. Destruction of angle of left mandible with dentigerous cyst anterior to area of rarification.

struction. A mass was present in the right parietal region, in the dura over the left frontal lobe, in the cerebellum near the pons, and over the great wing of the sphenoid. These masses were the same grossly as the ones already described. The kidneys were large, granular, and pale. The liver and spleen showed some congestion. The heart and lungs were negative. The anatomic diagnosis was right adrenal cell tumor with metastasis to the skull, vertebrae, long bones, mandible, brain, ribs, and lymph nodes—subacute parenchymatous nephritis.

Microscopic examination.—Sections of the tumors consisted of small cells with deeply stained nuclei. The cells were packed in groups with orderly arrangement; rosettes were present. There were circular aggregates of cells which showed mitotic figures. The cells lay in a fine granular matrix. The fibrillae could not be demonstrated. The microscopic diagnosis was neuroblastoma, subacute parenchymatous nephritis, cloudy swelling of the liver, spleen, and heart. A section from one of the metastatic growths revealed the same type of tumor.

X-ray studies.—On July 17 a plate of the left mandible revealed destruction of the angle with a cyst in the region of the third molar. Two days later a lateral plate of the frontal area showed periosteal thickenings and striations. On July 22 a plate of the femurs and humeri showed feathering of the epiphyseal ends. On

Fig. 2.—Further destruction of tibia and femur at epiphyseal ends.

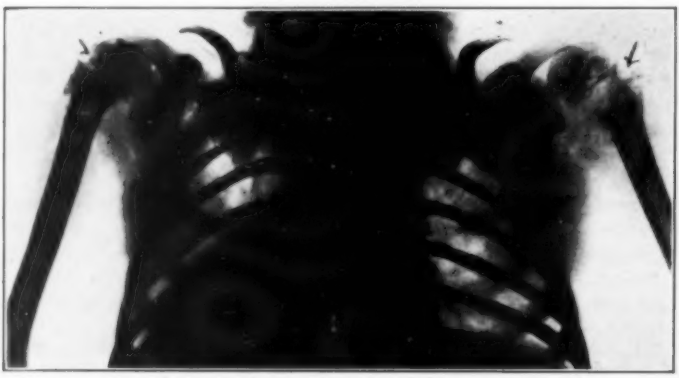

Fig. 3.—Pathologic fractures of proximal epiphyses of the humeri, with marked destruction.

Fig. 4.—Metastasis to left side of frontal bone showing feathering of the periosteum.

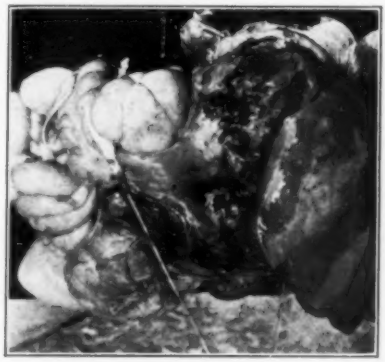

Fig. 5.—Gross specimen of tumor.

August 9 a lateral plate of the frontal bone revealed an osteogenetic process with new bone formation. A plate of the humeri at the same date revealed marked destruction of the proximal epiphyseal ends. At this date a dentigerous cyst of the right mandible in the region of the third molar was described. On August 10 plates of the long bones revealed fractures of the proximal ends, with marked destruction.

COMMENT

This case is presented because of the interesting features; the variation in the metastasis of a tumor from the right adrenal is worthy of report. The involvement of all of the long bones with fractures is of interest.

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828 Medical Arts Building

Pediatric Clinics

THE CHILDREN'S MEMORIAL HOSPITAL, CHICAGO

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CUSHING has aptly said, "Hospitals have personalities." The chief aim of this series of special articles, as I take it, is to portray the personality, the individuality, of each clinic or hospital described. Because of its isolation as a self-centered and independent institution, the Children's Memorial Hospital lends itself peculiarly to this approach. The name of the Hospital itself conveys one important phase of its personality. With one exception, all of the buildings devoted to the care of children and to the housing of the resident and nursing staff have been erected as memorials. This in itself constitutes a background of human interest and sentiment of which those interested in its conduct cannot be unmindful. Originally established as a charitable institution, it has remained almost wholly so throughout its fifty years of existence. In 1926 provisions were made for the admission of private patients as well in one wing of the newly erected Martha Wilson Memorial Pavilion. The chief interest in this departure lay in providing for concentration of the work of the medical staff in one place, rather than in an added source of income. About 60 per cent of the operating expenses of the Hospital are met with income from endowments, largely from bequests. The balance is almost wholly supplied by general or special bequests, by annual contributions of those interested in the Hospital, by the proceeds from a Rummage Shop, and in the last two years by contributions from welfare and relief agencies. Last year less than 10 per cent was received from all patients and only about 5.5 per cent from the out-patient clinic and ward patients. The Hospital has been able to weather the economic depression with only minor curtailment of some service and of salaries in spite of an enormous increase of attendance in the Out-Patient Department.

The general direction of the Hospital is vested in a Board of Trustees of seventeen members. The Board of Trustees appoints annually the medical staff, the Superintendent, the Directress of the Training School, and a Women's Auxiliary Board of some forty-six members, who are responsible for the internal administrative management of the Hospital. In order to effect a closer and more prompt cooperation between the various agencies that take part in the conduct of the Hospital the following committees have been established, each to meet once a month:

1. The Superintendent, the Chief of Staff, the Directress of the Training School, and two other members of the medical staff appointed by the Chief.
2. The Superintendent, the Chief of Staff, the Medical Director of the Out-Patient Department, and the Head of the Social Service and Nursing Staff of the Out-Patient Department.
3. The President of the Board of Trustees, the Superintendent, the Chief of Staff, the President of the Women's Auxiliary Board, and two other members of the Board of Trustees appointed by the President. Other members of the staff are asked to attend these meetings as seems desirable.

Seven of the eight buildings that constitute the Hospital are arranged on the pavilion plan around the periphery of a roughly triangular grass plot of four acres, facing chiefly on Fullerton Avenue, but also on Orchard Street and Lincoln Avenue, about three miles distant from the downtown section of the city. North of Fullerton Avenue stood the original Maurice Porter Memorial Hospital of thirty beds, founded in 1884 by Mrs. Julia F. Porter in memory of her son, Maurice Porter. The growth and development of the Hospital can best be followed from this point on by a description of each new building in chronologic order and by references to the accompanying illustration taken from about the middle of the Hospital grounds.

The Maurice Porter Memorial Pavilion, the two-story building with solaria, near the center, was donated by Mrs. Julia F. Porter in 1908. The first floor has thirty-two beds for orthopedic patients, the second floor a like number of beds for patients with rheumatism and its complications and sequelae, and nephritis.

Cribside Pavilion, the smaller two-story building on the extreme right, was donated by the Cribside Society of the Hospital in 1908. It has thirty beds for medical and surgical patients under eighteen months of age. The lower floor is divided into cubicles and is used exclusively for infants with infections. The upper floor is reserved for those free from infection. The diet kitchen for infants is in the semibasement.

On the extreme left is the Agnes Wilson Memorial Pavilion donated by Mr. John P. Wilson, Sr., in 1912. Originally occupied by wards, it was remodeled in 1926 to accommodate the growing Out-Patient Department. In the semibasement are the record room for the whole Hospital, the x-ray laboratories, the drug room, and isolation and hospital admitting rooms. The first floor contains the main Out-Patient Department admitting room, the social service quarters, two preparation and waiting rooms, and three examining rooms, all exclusively for babies. On the second floor is a secondary receiving room, a preparation room, and eleven examining rooms. The third floor contains the chemical, bacteriologic, clinicopathologic and Otho S. A. Sprague Memorial Institute laboratories, the morgue and autopsy rooms, a museum, and a large room for photography and basal metabolism determinations. On the roof is a penthouse for animals with outdoor runways. Immediately next to this building is the one- and two-story building with twenty beds for patients with contagious diseases arising in the Hospital. The semibasement is used by the Psychiatric and Speech Correction Departments. Between, and connecting, the two buildings is a clinical amphitheater seating about sixty-five.

The Martha Wilson Memorial Pavilion, the larger five-story and semibasement building shown on the far right of the illustration, was completed in 1926 "under the provisions of the will of Martha Wilson and out of the proceeds of her residuary estate." It was a part of her vision, characteristically expressed in this manner, that provisions for private patients should be made, with the main thought in mind that it would accrue to the benefit of the volunteer staff of the Hospital as well as to that of the Hospital itself. The basement contains the general and special kitchens, the library, the central supply room, store-rooms, etc. The main portion of the building faces Fullerton Avenue and from this a wing extends along Orchard Street. On the first floor the main portion houses the administration and the nursing staff; the wing, waiting and admitting rooms and doctors' rooms. The second floor has in the main portion thirty-one beds for medical patients and in the wing eight rooms devoted to a Health Service and Infirmary for temporary illnesses of the nursing and interne staff. The third floor has a like arrangement with thirty-three beds for surgical patients in the main portion and eight private rooms for the use of the staff and any other accredited

physician. On the fourth floor are two operating rooms, sixteen beds for tonsil and adenoid patients and nine beds for oral surgery. In the wing of this floor are twenty beds in two- and four-bed private wards for the exclusive use of the attending staff. On the roof are accommodations in two large and two small rooms for twelve boys and twelve girls, with a large open space in each wing into which the beds can be wheeled. The patients are largely subacute or chronic cases transferred from the medical, surgical and orthopedic floors. There is also a large play room and a therapeutic tank.

In 1931 the original Hospital building on the north of Fullerton Avenue was torn down, and on an enlarged site the nurses' and internes' seven-story residences were completed and occupied. These buildings were erected in memory of Nellie A. Black and James Deering, respectively. Accommodations are provided in these buildings for 142 nurses and twenty-one internes and residents. The nurses' home contains an auditorium seating 300. It is connected with the other buildings by a tunnel. With the completion of these buildings the original nurses' home at the apex of the triangle was remodeled and is now occupied by the help. The only other building is a large power and light plant and laundry

View of part of the Children's Memorial Hospital from the middle of the Hospital grounds. The buildings from left to right are the Contagious Pavilion and Out-Patient Department (Agnes Wilson Memorial); the Maurice Porter Memorial Pavilion for orthopedic, cardiac, and nephritic patients; the Martha Wilson Memorial Pavilion for older medical and surgical, and private patients; and the Cribside Pavilion for infants under eighteen months of age.

to the left of the contagious building on Lincoln Avenue. This was erected in 1931 "with funds made available by contributions of friends of the Hospital."

The university affiliation and teaching activities of the Hospital are rather unique. "Toward the close of the year 1919 an agreement was reached between the University of Chicago and the Children's Memorial Hospital for affiliation of the Hospital with the University. This does not mean that there has been in any sense or to any degree a merger of the Hospital in the University. In the preamble of the agreement it is expressly stated that the provisions of the contract are 'the basis of affiliation and cooperation under which relations between said two corporations shall be entered into and maintained, each corporation expressly retaining and maintaining its several responsibilities and sole and separate obligations with respect to the carrying out of the purposes for which it has been organized. . . . This agreement is terminable at the election of either party upon one year's notice.'" The original purpose was "to make the Children's Memorial Hospital a center for postgraduate work in the study and treatment of diseases of children." Delay in completion of the University Clinics, a distance

of ten miles between the two institutions, and other considerations have made the affiliation nominal rather than active. Postgraduate work, in the usual sense, has been restricted to one or two annual courses of one month each for practitioners. In a very real sense the staff feel that their most important postgraduate interest and activity center in the interne and resident staff. Since 1931, without formal affiliation of any kind, the Hospital has furnished clinical instruction to seniors and juniors of the nearby Northwestern University Medical School. Two amphitheater clinics a week are conducted each quarter, one for juniors and one for seniors, each class numbering from twenty to twenty-five. Throughout the year from eight to ten seniors attend the Out-Patient Department clinics daily for one month, and two or three clerks are assigned to the wards for a like period.

Since 1920 the medical and surgical staff have been made up of a Chief of Staff, or medical director, a few part-time members, and a much larger number whose service is voluntary. In 1930 the Chief was placed on a practically full-time basis, except for the privilege of doing a limited amount of private practice. All members of the staff are appointed annually. The Chief, upon notification of his reappointment, recommends to the Trustees of the University of Chicago all of the medical and surgical staff for the ensuing year. After they have been acted upon by the Trustees of the University, they are in turn acted upon by the trustees of the Hospital. The attending staff consists of about ninety members distributed as follows: fifty pediatricians, three neurologists, one dermatologist, seven general surgeons, three orthopedic surgeons, three oral surgeons, two neural surgeons, two urologists, eight otolaryngologists, one endoscopist, four ophthalmologists, one pathologist, one roentgenologist, one speech corrector, two dentists, and one resident director of the Otho S. A. Sprague Memorial Institute. In addition to the last five enumerated there are also part-time directors of the Out-Patient Department and of the Hospital Health Service.

The resident staff consists of two medical residents, one in the wards and one in the Out-Patient Department, a surgical resident, and a resident in pathology, the latter maintained by the Sprague Institute. There are eleven internes who rotate through all services including the Out-Patient Department and the surgical specialties. The deficiency of a newborn service is in part met by a service at the nearby St. Joseph's Hospital. No apology is offered for a rotating service since all work with children is of about equal pediatric interest and importance. A preceding year of a rotating interneship is required of internes and an additional year of pediatric work of residents. The internes do all of the ordinary routine laboratory work. The resident in pathology performs all necropsies and conducts the weekly pathologic conference. There are about 175 necropsies a year. The usual attendance at the conferences is about forty. Particular emphasis is laid on correlation of the clinical, roentgenologic, and gross pathologic findings at these conferences.

The Children's Memorial Hospital is primarily a clinical institution, and stresses that phase of pediatrics. This is a part of its personality, and follows to some extent from the nature of its organization, its isolation, and its material. The staff, attending and resident, feel that the care and study of sick children and their own clinical development are fundamental to all pediatric activity. Research, and especially that of the laboratory, is not featured to the extent that it is in some clinics and is not encouraged in those who show no initiative or interest in that phase of pediatrics. To those who do, every opportunity, encouragement and stimulation is given. Because of the nature of the organization and the rather ample material, investigation is chiefly along clinical lines. The

Otho S. A. Sprague Memorial Institute under the general direction of Dr. H. Gideon Wells has been an important factor in the research activities of the Hospital for over twenty years.

Perhaps an outstanding phase of the Hospital's personality is its activity, one might say interest, in Out-Patient Department work. Nearly 85 per cent of the staff does some work in the Out-Patient Department. Nearly all of the internes and residents consider it the most valuable part of their hospital experience. It is treated as of at least equal importance in every respect with the rest of the Hospital. The two activities are so interwoven that there is no sharp line of cleavage. The Out-Patient Department is a part of the daily rounds. The Hospital with 264 beds has had for some years about the same average daily occupancy, somewhere around 180. The annual out-patient visits on the other hand have increased in the last six years from 27,932 to 70,519. While this increase, especially in the last two years, is in part due to the prolonged economic depression, this is largely neutralized by the strenuous efforts of clinicians and especially of the social service unit to limit attendance along geographic and other lines. Every effort is made to cooperate with outside physicians and whenever possible to refer patients to their own physicians both at the beginning and at the end of their attendance in the clinic. A careful social and financial history of each patient is obtained as a basis for admission or rejection from the clinic. Our present physical equipment is not adapted to the care of well babies, and all such are referred to infant welfare stations who in turn consult with, and refer sick babies to, the clinic. A very efficient social service and nursing staff plays an indispensable part in the conduct of the clinic. Nearly every larger special clinic has its own social service worker. A large corps of volunteer workers contributes to the work of the clinic by weighing and preparing patients, especially babies, for examination, by bringing patients to the clinic, and by serving as writers for clinicians.

ATTENDANCE AT SPECIAL OUT-PATIENT DEPARTMENT CLINICS IN 1933

Department	Patients in Clinics	Visits to Clinics
Infant Clinic	2,118	5,377
Medical Clinic	11,979	23,543
Quartz Light Clinic	11	63
Urology Clinic	235	788
Cardiac Clinic	741	2,025
Neuropsychiatric Clinic	599	2,332
Surgical Clinic	2,886	8,193
Orthopedic Clinic	928	4,879
Dermatology Clinic	634	1,688
Ear, Nose, and Throat Clinic	2,991	6,773
Eye Clinic	2,511	7,447
Syphilitic Clinic	593	2,949
Speech Clinic	103	932
Sprague Laboratory	262	386
Asthma Clinic	250	2,470
Oral Surgery Clinic	114	367
Diabetic Clinic	24	247
X-ray Treatments	27	60
Patients registered in clinic for 1933	Total	18,589
Visits made to clinics in 1933	Total	70,519
Number of free visits* to clinic in 1933	Total	52,418
Number of desk interviews in 1933	Total	27,397

*By "free visit" is meant that the patient cannot pay twenty-five cents.

Special clinics are conducted in the usual subjects, and by the same clinician, both in the Out-Patient Department and in the wards. The nature of these and the attendance, as shown in the following table, may be of interest.

What has seemed to us an interesting feature has been the low occupancy of our infant wards as compared with that of many other hospitals. For reasons that are probably patent to every pediatrician it is our aim to keep out, rather than to admit, all babies that can be cared for reasonably well or better outside of the wards. In a general way this policy applies also to older children unless they are of unusual clinical interest. With provision for thirty babies in Cribside Pavilion our average occupancy is around 50 per cent and sometimes falls to 25 per cent. Only about 9 per cent of the total occupancy of the Hospital comes from infants under eighteen months of age. Having no interest in per capita cost, in full wards per se, or in the dubious pedagogic value to the interne and resident and nurse of mass experience in morbidity and mortality in an infant ward, this is as we want it. The efficient service of the Infant Welfare Society, and of our own Out-Patient Department is possibly an important factor in being able to bring about this result with a definitely lessened morbidity and mortality rate. There are doubtless climatic, social, and other factors that enter into the picture, but they are not evident on the surface. There is no convalescent home service available to the Hospital for the care of babies and only to a limited extent for older children. Our interest in recent years has steadily increased in an apparently safer, better, and cheaper foster-home convalescent care for both babies and older children.

Critical Review

INFECTION AND IMMUNITY

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INTRODUCTION

THE subjects of infections and immunity have become so involved that it will be necessary to review cursorily their more fundamental principles in order to understand properly the conceptions that are mentioned in the medical literature. It is equally obvious that one must have an understanding of the many terms used to describe these ideas. For convenience, I will discuss the topic under the following heads:

I. Infection.
II. Immunity.
III. Hypersensitivity as a Result of Passive Immunity.
IV. The Application of Principles of Infection and Immunity to Specific Diseases.

These topics shall be considered only as they apply to man as a host, though we may utilize knowledge derived from correlated and other species for purposes of illustration. The subject matter may be found covered in detail in any of the textbooks by Karsner and Ecker,[1] Zinsser,[2] and Kolmer.[3]

I. INFECTION

We have progressed a little from the days when our progenitors argued as to whether diseases were caused by mechanistic or vitalistic actions or were the result of fermentation or of spontaneous generation, miasmic factors, etc., to the conception of today that infection is the result of metabolic processes of organisms that utilize the living tissue of a host for their growth and survival.

It is fundamental at the onset to appreciate the difference between contamination and infection. A thing may be grossly contaminated with organisms and yet no infection be present. On the other hand, infection may occur with contamination. In a general way, persistent contamination may sometimes bring about an increase in resistance against the specific contaminating organism. It is impossible to be dogmatic as to what is and what is not contamination in certain parts of the body. For example, the presence of diphtheria organisms in the throat does not necessarily mean a diphtheritic infection. At times, these organisms may be merely leading a saprophytic existence in individuals who have previously had the disease, or they may be contaminants, but subminimally parasitic enough gradually to build up an immunity in the host, even though the individual may be seemingly free from demonstrable infection.

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The sequence of infections may be important. An organism may be the primary or secondary cause of a disease process, the latter really being a complication of the first. For example, the mortality rate for whooping cough is very high, yet when one analyzes the reasons for the cause of death in this disease, it is found that secondary bronchopneumonia accounts for the greatest percentage of the high mortality rate. Multiple secondary infections may occur that are totally unrelated to a primary infection, and it is obvious that in a series of infections, the terminal one is usually the cause of death. Such terminal infections if primary might not be fatal.

Infections may be epidemic or endemic in character and peculiar to well demarcated localities or general in their spread.

Some organisms will produce specific local reactions in the host. Others will be specifically local in their growth, but because of their metabolic activity, cause remote symptoms in the host. Some of the latter are called focal infections. On the other hand, some infections may involve all the organs of the body, irrespective of the original focus or portal of entry, and if the host has no protection or immunity the damage may be massive and the issue quickly decided. These infections are called fulminating or malignant. Children of the civilized world do not die as a result of measles per se, but because of the secondary infection of bronchopneumonia. The fulminating type of measles occurs rarely save in races that have never been previously exposed to the infection. One must never forget that some of the more usual diseases to which we have become accustomed are apt to evince malignant manifestations in virgin soil. It must be remembered likewise that diseases which for years have been mild in character may suddenly become malignant.

The human host through long years of exposure had adapted itself so that the entodermic and ectodermic coverings of the body prevent the ingress of the ordinary bacteria that could attack the vital hidden parts beneath. A break in the host's defense mechanism will provide an entrance through which organisms may come in contact with tissues not prepared to meet the onslaught of the invader. Streptococci on the skin are harmless to the host. Streptococci in the corium or subcutaneous tissue mean an infection with organisms that are usually destroyed in situ if the patient is to recover. It is important to know the portal through which an organism gains access to the undefended tissue since symptoms usually begin there as a part of a clinical syndrome. Certain diseases have a regular or usual portal of entry. It is quite true that diphtheria bacilli may lodge anywhere in the human host and cause infection, but the usual infection occurs in the upper respiratory passages. If we know the portal of entry, we usually know the site where the host first complains of symptoms, and we can sometimes guess the genus of the offending organisms.

As a result of infection, several conditions may develop, dependent upon the patient's resistance. The offending organisms may multiply to the extent that they enter the blood stream; bacteremia will then develop. The disease may cause such an increase in the white cells of the blood elements that abscesses and pyemia will result. The organisms may shunt their metabolic products into the blood stream to be carried everywhere, resulting in a toxemic condition in the host. An individual's resistance may be so lowered by one infection that ordinary saprophytic organisms may actually multiply in the blood stream and sapremia be found; finally the bacteria may multiply to such an extent

that, with their toxins, a condition of septicemia may be noted. The terms, toxemia, septicemia, moribund and septic, are not such as to lend themselves well to actual definition. Word pictures and all the adjectives at one's command do not convey to a person who has never seen such a case the correct impression as to just exactly what is meant by these terms. We recognize these conditions only after we have seen the clinical entity.

After the onset of an infection in the host, a train of events follows which is often predictable since it may have a definite pattern peculiar to the particular organism that has caused the infection.

Infection itself may be broadly defined as the result which is brought about in the host by the metabolic processes of an organism or as the derangement in the host, either local or general, that results when organisms have passed through a portal of entry in the host and have gained access to susceptible tissue.

Though organisms may break through a portal of entry, their spread depends upon their virulency and the susceptibility of the host. The former could be roughly defined as its disease-producing power, which under various conditions may be enhanced or modified, as will be noted in subsequent paragraphs.

Bacteria must have a favorable tissue in which to multiply before they can become dangerous. Some sites in the host are peculiar in that they are inherently antagonistic and tend to limit the growth of certain organisms to a relatively innocuous saprophytic existence. The presence of the colon bacillus in the large intestine is unimportant from an infective standpoint; in fact, its presence is almost a necessity to the host from the point of view of metabolism. On the other hand, when this organism locates elsewhere, it becomes parasitic and can cause disease, as it does in pyelitis.

The virulence of an organism may not be lessened, but, because it is implanted on a site unfavorable for its particular growth, it may not be able to cause disease, whereas it is just as true that the soil upon which an organism lives may be so favorable as to enhance its growth and often its virulence. Vincent's organisms, really facultative anaerobes, do not grow well on the skin or, ordinarily, in the vascular muscular tissue since the latter is well oxygenated, but they will grow luxuriantly in crypts of the tonsils and in areas between the teeth and gums where oxygen may be excluded. This point is nicely illustrated when Vincent's angina attacks the tonsils. These glands may be entirely destroyed by the infection, but the disease usually stops when the infection reaches the capsule and the muscular tissues beneath the gland, irrespective of the type or kind of treatment, chiefly because of the fact that the organisms have reached an unfavorable place for their multiplication.

Some species may be susceptible to organisms that do not infect other species. For example, the human being is extremely susceptible to infection by the streptococci while chickens are not. Such information is chiefly important from an experimental and epidemiologic standpoint.

Marked differences appear in the same classes of bacteria that cause infection. There are smooth and rough strains of virulent bacteria, so-called because of the way they grow on artificial media. The smooth strain is usually more virulent and pathogenic while the rough is often avirulent and nonpathogenic. Some disease irritants are so small that they can pass through finely graduated filters. Such entities are called viruses.

In the growth of an organism, just as in the growth of any living thing, multiplication depends upon the presence or absence of light, moisture, carbon, nitrogen, oxygen, certain salts and denatured proteins or certain particular elements such as hemoglobin, etc., as the case may be. Although all of these enumerated factors necessary for growth may be present, still these organisms may die because of the unfavorable temperature at which incubation occurs.

The number of bacteria that gain access to the host at any one time is important in the consideration of any infection. Broadly speaking, immunity to disease is merely that protection which prevents an individual from contracting the infection under the ordinary circumstances of exposure. Irrespective of protection, disease may come about when the host is exposed to massive doses of organisms, though the inherited or acquired protection may be sufficient to modify the severity of the disease attack.

By far the most important characteristic of an organism from a disease-producing standpoint is its capability of defending itself against the opposing factors of the host. It is obvious that if the organisms cannot live and multiply at the expense of the host, they cannot produce disease. One must remember this fact when considering all of the forces brought into play by the organisms to overwhelm the defense of the host.

Even though an organism may be virulent, it depends in great measure for its growth upon a favorable host. A host that is unfavorable may be made experimentally favorable. The frog, a thermolabile species, will not be affected by anthrax in its natural state, but, if its temperature is raised to or above that of the human, it may be infected.

There are certain organs of the body in which bacteria may multiply better than in others; in other words, there is manifested a specific susceptibility on the part of an organ. It is also true that there are organs which have a heightened specific resistance against certain bacteria.

Although the organisms may gain access to the host or reach a susceptible organ in such numbers as would ordinarily cause a disease, they must have time to multiply in these favorable areas before the alterations that are produced in the host are recognized as disease. An undisturbed incubation period, then, of a relatively shorter or longer time is an absolute essential in order to enable the organisms to produce the disease in the host. It may take a long while to bring about typhoid fever. On the other hand, the organism that causes scarlet fever may multiply sufficiently to cause the disease within from 24 to 48 hours.

Although many organisms are able to produce disease by mere extension and multiplication in the tissues of the host, there are peculiarities about the metabolic activities of some organisms that make them distinctive. Certain bacteria produce poisons, some of which are contained within the cells and are only released at the death of the bacteria. These are called endotoxins. Others produce poisons or toxins while still living in the host. This type of poison is called extracellular, or an exotoxin, or it is described as a true soluble toxin. Often the bacteria themselves, as is the case with diphtheria, do not cause any essential harm and were it not for the extracellular toxins produced by the organisms, they would be relatively innocuous. Often the endotoxic or exotoxic poisons or themselves have peculiarly specific qualities. They may have the property of cytolysis; that is, they are capable of dissolv-

ing the cells of the host; hemolysis and cause lysis of the red cells; leucocidins and kill the leucocytic cell; hemaglutinins and agglutinate the red cells; aggressins and paralyze the protecting agency in the cell body, as a consequence of which the host is overwhelmed; virulins and inhibit phagocytosis. (The evidence as to the presence of the latter two entities is debatable since both poisons might very well fall under the general head of endotoxins or exotoxins.)

Bacteria may often cause metabolic changes by fermentative reactions. The disease condition in the human is due not always to the organism or its endo- or exotoxic products. Sometimes the metabolic reactions that result after the cells of the host have absorbed the dead bacterial proteins are sufficient to disturb the balance of normality and produce a disease picture. Some of the poisonous products of bacteria are common enough to receive specific names such as staphylotoxin, diphtheria toxin, streptoxin, tetanus toxin, botulinus toxin, etc. Phytotoxins and zootoxins are evolved by a higher order of species than bacteria and are not considered in this review.

II. IMMUNITY

For a long time there were two schools of thought as to how immunity was produced. Metchnikoff hypothecated that protection and subsequent immunity were brought about by the action of the cells of the host. The other school with Flügge held that protection was a humoral thing, the result chiefly of fluid tissue changes. At present, it is obvious that immunity and the protection that follows are effected by both cellular and humoral reactions with the aid of many other processes about which little or nothing is known.

The cellulist stated that when organisms passed the portal of entry, the leucocytes or lymphocytes were brought to this area as a result of some chemotactic influence, the result perhaps of osmosis or diffusion. The white cells (leucocytes) were massed as an army at the site of the infection. They engulfed the bacteria which they sometimes killed outright by themselves or with the aid of enzymes contained in the leucocytes, and sometimes they merely incarcerated the organisms for the time being. In the latter case, if the white cells were later destroyed, the bacteria would be set free and could again begin multiplying. Metchnikoff thought that an individual was immune to an infection if he possessed leucocytes in the tissues that functioned, and that the acquisition of immunity was accomplished by training the leucocytes to perform more ably what he considered their natural function. If the leucocytes were not destroyed, the macroblasts might engulf them, together with all the local débris. These large wandering cells may actually prevent the death of an animal after the injection of virulent organisms. Whether they come from fixed tissue cells or are white cells which have become differentiated need not bother us in this review. Though the question is not settled, the contention today seems to be that they are part and parcel of the reticulo-endothelial system. No matter by what name they are called—histocyte, clasmatocyte, giant cell, fixed tissue cell, etc.—their major function in an infection seems to be that described by Metchnikoff as peculiar to the macrophage.

A rabbit injected intrapleurally with a mixture of streptococci and broth will die. If a broth mixture is injected into the pleura, there is a local increase in clasmatocytes. If a fatal dose of streptococci is given intrapleurally two days after broth has been injected, the animal will

survive. When peptone broth applications are placed on the abdomens of guinea pigs, elasmatocytes are found increased in the subcutaneous area. When staphylococci are injected locally in doses that are usually fatal, the animal may develop nothing more than a localized inflammatory response. The controls may die, even though the number of small white cells found about the local lesions in their skins is legion. These defensive cells of the blood are protean in their avidity for foreign particles.

Many of the local immunities seem to be nonspecific in type.

When infection occurs, another type of immunity, the humoral, may be perfected. This is evidenced by the presence of so-called antibodies in the bodily fluids; of precipitins which precipitate the antigen; agglutinins which clump the organisms; bacteriocidal elements; bacteriolytic antibodies which dissolve the bacteria; lysins; enzymes; cytases which dissolve cell walls; antihemolysins, substances which prevent solution of the blood cells; antiferments; tropins which exist in immune serum and aid phagocytosis by acting on the bacteria, particularly antitoxins which neutralize the toxins; and antitryptic elements which, in general, hamper or completely inhibit bacterial growth.

As was stated before, immunity is brought about by a combination of forces, both humoral and cellular. Which type of immune principle would be most involved in a particular disease depends upon the character of the invading organism. The antitryptic elements present in normal serum may hamper, kill, or have no defense against an organism. In the latter instance, the battle for recovery is left to the phagocytes, and the bacteria involved are termed serophytic since they grow in normal serum. Staphylococcus, streptococcus, and pneumococcus are good examples of such organisms. Other organisms may not be killed, but are hindered in multiplying so that phagocytosis may not be hampered. If the serum of such a patient loses its antitryptic character, the efficiency of the phagocytes may be lessened. It can be seen then that immunity is actually a combination of forces, cellular, humoral, etc., so that when one element is neutralized, the other elements are apt to be lessened in their efficiency.

The exact spot where the humoral antibodies are manufactured is usually unknown, but it may be selective or organ in type, for example, the skin, the gastrointestinal tract, etc. Thus it may be local and strictly confined to one place, or it may be general and the entire body concerned in its production.

Protection of the host against the invading organisms or their products is helped by immunity. The latter term could be defined as that inherent something which an individual possesses that protects him from attacks of disease. In general, immunity may be natural or acquired. If acquired naturally, it may be a characteristic something possessed by a species, as we have seen with frogs that are not susceptible to anthrax, or it may be a racial immunity or a lack of immunity. A racial lack of immunity to tuberculosis exists among members of the Negro race. It may be a familial immunity which tends to protect whole families against infection; or it may be individual in character, whereby certain members of a family may have more protection against infection than others of the same family; or it may be inherited from the mother, as it is in measles. Species immunity is interesting simply from an experimental standpoint; and of the other types of natural immunity, the in-

herited is the only one of practical importance. Inherited immunity is merely relative since such immunity can be broken down if the numerical number of invading organisms or infecting units that attack the host are more than sufficient to neutralize the antibodies present.

The acquisition of immunity may be natural, occurring as a result of an attack of a disease. If the host survives the original attack, there are usually no further infections of the same character. The search for methods of artificially developing immunity forms the basis for practically all advances in immunology and for much of the experimental work done in medicine for the past fifty years. All immunization programs have as their object the production of qualities in the susceptibles which neutralize, precipitate, or destroy the bacteria or its poisonous substances.

Artificial immunity in the host may be acquired either actively or passively. Many people confuse these terms. Active artificial immunity is acquired by a susceptible person after he has in some way been given a modified attack of the disease. Passive immunity artificially acquired, on the other hand, is a temporary immunity conferred upon an individual who already has the disease in an attempt to neutralize the effects of the acute infection. The serums or antitoxins used to develop this type of immunity (passive) are obtained from persons or animals that have recovered from the same infection or from animals that have been actively immunized against the infection. Passive types of immunity are fleeting in character and merely tide the patient over a crisis.

There are four methods of acquiring active artificial immunity. One is by the injection of the very material that causes the infection. This the Chinese did when they protected against smallpox by practicing variolation. By this procedure, some of the pus from a pustule was taken from an individual who had a mild attack of smallpox and inoculated into susceptible persons in the hope that the latter would get mild attacks of the disease. One can easily surmise that, since the virulency of the virus and the susceptibility of the host were unknown factors, the results were unpredictable, and that many times the individuals whom they tried to protect died from the very disease that resulted from the attempted immunization. One should not confuse variolation with the present method of vaccine virus vaccination, for the former method of acquiring artificial immunity has been forbidden by the laws of all civilized countries since the middle of the last century.

Another method of artificially acquiring immunity is by the injection of attenuated living organisms, virus, etc. Pasteur found that when the germs of fowl cholera remained on the shelf in his laboratory for three months or so, they lost much of their pathogenicity but retained their antigenic value and their capabilities for producing immunity. As a result of this experience, many advances in medicine were made possible.

A third method of artificially protecting humans is by injecting the killed bacteria that cause the disease; the best illustration of which is seen in the use of typhoid vaccine. The fourth method is to inject small amounts of the bacterial poisons that cause the disease. This is done in protecting against diphtheria.

Specific serums, convalescent serums, or antitoxins are used to give artificial passive immunity to the sick patient. It may be repeated that such injections only protect temporarily if at all. A person ill with

TABLE I

DISEASE	CONTAGIOUS INDEX FOR HUMAN BEINGS	SPREAD BY DIRECT OR INDIRECT CONTACT WITH HUMAN BEINGS	NATURAL IMMUNITY		ACTIVE ARTIFICIAL IMMUNITY			PASSIVE ARTIFICIAL IMMUNITY		SPECIFIC TESTS FOR SUSCEPTIBILITY
			PRESENT BEFORE DISEASE ATTACK	ACQUIRED AFTER DISEASE ATTACK	METHOD OF ACQUIRING	SUCCESS	DURATION	TYPE FOR ACUTE ATTACKS	SUCCESS	
Anthrax	variable	both	none	yes	vaccine	variable	variable	anthrax serum	poor	none
Chickenpox	high	both	none	yes	no method	(−)	(−)	none	(−)	none
Cholera	high	both	none	yes	vaccine	dubious	questionable	cholera serum	poor	none
Diphtheria	low	usually direct	inherited slight	yes	T-antitoxin or toxoid	excellent	8 yr. + ?	diph. antitoxin	good	Schick
Encephalitis	low	probably direct	?	?	no method	(−)	(−)	conval. serum	?	none
Erysipelas	low	questionable	none	none	no method	(−)	(−)	ery. antitoxin	questionable	none
Glanders	low	probably direct	none	yes?	no method	(−)	(−)	none	(−)	Mallein test
Leprosy	low	probably direct	?	probably none	no method	(−)	(−)	none	(−)	none
Measles	high	both	inherited lasts 4—6 mo.	yes	no method	(−)	(−)	conval. serum	good	none
Measles—German	moderate	probably direct	same	yes	no method	(−)	(−)	none	(−)	none
Meningitis epidemic	low	direct	individual	same	no method	(−)	(−)	meningitis serum	fair only	none
Mumps	moderate	direct	none	yes	no method	(−)	(−)	none	(−)	none

TABLE I—CONT'D

DISEASE	CONTAGIOUS INDEX FOR HUMAN BEINGS	SPREAD BY DIRECT OR INDIRECT CONTACT WITH HUMAN BEINGS	NATURAL IMMUNITY		ACTIVE ARTIFICIAL IMMUNITY			PASSIVE ARTIFICIAL IMMUNITY		SPECIFIC TESTS FOR SUSCEPTIBILITY
			PRESENT BEFORE DISEASE ATTACK	ACQUIRED AFTER DISEASE ATTACK	METHOD OF ACQUIRING	SUCCESS	DURATION	TYPE FOR ACUTE ATTACKS	SUCCESS	
Plague	high	both	none	yes	Haffkine's vaccine	variable	variable	anti-plague serum	poor	none
Poliomyelitis	low	unknown	individual	yes	none	none	(–)	conval. serum	poor	none
Rabies	variable	direct	probably none	yes?	Pasteur's treatment	good	questionable	none	(–)	none
Scarlatina	35-65%	both	inherited lasts 4—6 mo.	yes	Dick toxin	good	2-4 yr. ?	s. f. antitox. conv. serum	questionable	Dick
Smallpox	high	both	none	yes	vaccination	excellent	5-7 yr. ?	none	(–)	none
Tetanus	variable	direct	inherited slight	?	tetanus toxoid (Park)	good	questionable	tetanus antitoxin	good	none
Tonsillitis—acute strep.	high	both	individual slight	none?	vaccine mixed	variable	one season	strep. serum	poor	none
Trench fever	high	indirect (louse)	none	none	no method	(–)	(–)	none	(–)	none
Typhoid	moderate	both	individual slight	good	typhoid vaccine	excellent	2-3 yr.	typhoid serum	poor	none
Vincent's angina	low	direct	?	none	no method	(–)	(–)	none	(–)	none
Whooping cough	moderate	chiefly direct	none	yes	pertussis vaccine	variable	?	conval. serum	questionable	none

diphtheria who has been given diphtheria antitoxin may again contract the disease within a few weeks after a previous attack.

III. HYPERSENSITIVITY AS A RESULT OF PASSIVE IMMUNITY

The subject of hypersensitivity has acquired some importance because of the common use of therapeutic antitoxins, serums, etc. An individual treated with an antitoxin may react to the proteins contained in a therapeutic serum and is then said to show hypersensitivity.

A person's hypersensitiveness may be inherently natural, and he may be entirely ignorant of his sensitiveness until after the injection of a foreign serum when the reaction makes the condition obvious. On the other hand, the sensitivity may be acquired and the patient may have been made sensitive by the previous injection of a foreign protein, like serum. In this case, the history is of value.

After serum injection, the hypersensitive individual may have all grades of reaction from ordinary serum sickness to the most severe type of "anaphylactic shock." The latter term is usually reserved to describe persons who have been previously sensitized and who subsequently receive an injection of the sensitizing agent, after which shock and even sudden death may follow. Since this type of reaction occurs so rarely, one need not worry much about it.

Hypersensitivity in man is usually evidenced by a reaction to the therapeutic agent, which may be either immediate, accelerated, or normal in type. Patients who have immediate reactions may have one symptom or a combination of symptoms such as high fever, tachycardia, urticaria, joint pains, chills, vomiting, cyanosis, etc., all coming on within a time from a few minutes to a few hours after the therapeutic injection. The person who has an accelerated reaction will have the same type of symptoms, appearing later, however, approximately from 4 or 5 hours to 24 hours after the injection of the therapeutic agent. The delayed reaction is the usual type of serum sickness seen and appears from seven to eight days or more after the therapeutic injection. There are signs other than the rash which may indicate serum sickness, such as pain in the mesenteric glands, generalized glandular enlargement, arthritis, etc.

Sensitivity is determined by skin testing with a small amount of the therapeutic antigen. This is done either by scratching the skin, by the intradermal injection of the antitoxin or serum, or by the so-called ophthalmic test. It is my experience, after either making thousands of tests myself or having them done under my supervision in the contagious wards, that skin testing has no value in determining sensitivity to the various serums. My experience during the past two years has led me to conclude that the ophthalmic test is also of no practical value. We have found that there are just as many individuals who are positive skin test reactors and evince no evidence of hypersensitivity as there are individuals who are negative reactors and have serum sickness after the injection of the therapeutic antitoxin. I have come to the conclusion that we need not fear the therapeutic use of serums or antitoxins when administered intramuscularly and that skin tests are interesting experimentally, but they are worthless as far as practicability is concerned.

Attempts have been made to desensitize individuals who are hypersensitive by injecting increasing doses of the antigen (in this case, the therapeutic serum or antitoxin). The size of the initial dose depends upon whether the injection is to be intradermal, intramuscular, or intra-

venous. If desensitization is done intradermally, more antigen can be employed than if the serum were injected intravenously. Desensitization is invaluable in experimental work with animals, but, in my experience, it is worthless when applied to the human. In this connection, I wish to stress that I am not speaking of pollen antigens, etc., but only of therapeutic antitoxins and serums. We have had as many, and more severe, reactions in positive skin test reactors who were desensitized as we have in those who were not desensitized after the therapeutic antigen.

For the past fourteen years, a careful record has been kept at the Contagious Division of Cleveland City Hospital of the clinical reactions that followed the use of every tube of diphtheria and tetanus antitoxin and meningitis serum, and for the past few years records have been kept on every tube of scarlet fever and erysipelas antitoxin that was used on our wards. The patients still have serum sickness, though to a comparatively less extent, after the use of erysipelas antitoxin, whether the material has been super-refined or not; and we have reverted to our clinical practice of ten years ago and now pay little or no attention either to skin sensitivity or to desensitization.

IV. APPLICATION OF PRINCIPLES OF INFECTION AND IMMUNITY TO SPECIFIC DISEASES

We will now consider the practical aspects of some of the contagious diseases. The acute infectious diseases, the mycotic infections, etc., are to be reviewed by another writer. Such unusual things as psittacosis, rat-bite fever, etc., need not be discussed.

In referring to the diseases we have selected, the points to be considered will be as follows: the degree of susceptibility or the contagious index in humans; whether the spread of the infection is by direct or indirect contact; whether the human has any natural immunity because of race, inheritance, etc.; whether immunity is acquired as the result of a disease attack; the particular method of acquiring active artificial immunity and its success; the length of time this lasts if it is successful; whether the serums of individuals who have the disease contain antibodies or whether the serums of animals who have been artificially actively immunized contain protective antibodies that could be utilized in passive immunity; whether normal homologous human serum could be utilized and whether there is a method for testing out the presence or absence of immunity in the humans.

In Table I where the above outline is not complete, it shall be taken for granted that the points in question are obscure.

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American Academy of Pediatrics

Proceedings

THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MONDAY AFTERNOON SESSION
JUNE 12, 1933

Round Table Conference on Epidemic Meningitis

Leader: Dr. John A. Toomey, Cleveland, Ohio. Assistants: Dr. Albert J. Bell, Cincinnati, Ohio, and Dr. Edward B. Shaw, San Francisco, Calif.

The meeting was called to order in Room 191 of the Edgewater Beach Hotel at 2 P.M. by the Chairman, Dr. John A. Toomey.

Dr. Albert J. Bell opened the session by remarks on the "Bacteriology, Immunology, and Complications of Meningitis."

After the late war it might have been expected that there would be a very favorable condition for a world-wide spread of this disease, but this was not the case, save in one or two countries of which I will speak in a moment.

This (referring to Chart 1) represents the Union of Socialist Soviet Republics. The number of cases occurring, twelve thousand, is the largest number reported. This chart is from the Health Report of the Secretariat of the League of Nations, Geneva, March to April, 1932.

The second line represents the United States where the number of cases did not start to increase until 1926, reaching the peak in 1929.

England and Wales showed their initial rise in number of cases a year later, 1927, and reached the peak in 1931.

All other countries, except Germany and Japan, reached their peaks in 1929, 1930, or 1931. In Germany, as you see, the rise started in 1921 and reached the peak in 1922. Japan's increase started in 1923 and reached the peak in 1924.

France did not seem to show anything spectacular.

Chart 2 illustrates the trend of the morbidity of cerebrospinal meningitis in the United States from 1917 to 1931. This is also from the Health Division of the Secretariat of the League of Nations.

Epidemics occurred between 1917 and 1929. The disease was endemic all the time, but very sporadic in character. In 1929, we had our peak, and the morbidity curve decreased rapidly to 1931, as shown in the chart. I understand it was very much lower in 1932.

This map in the center gives a graphic distribution of the cases per hundred thousand of population.

In the shaded zones we see the greatest number of cases in Tennessee and Arizona. The next greatest proportion is in Indiana, Missouri, Alabama, North Dakota,

and Wyoming. Next in number of cases are the New England states and North Carolina. The epidemic skipped South Carolina and Georgia and caught Ohio, West Virginia, Virginia, Minnesota, Montana, and Nevada. Washington and California are also in this small group.

Kentucky, South Carolina, Texas, and Oregon have few or no cases.

I think this map shows clearly the apparent purposeless scattering of case distribution.

The table from McCoy* illustrated the actual morbidity rates. The greatest number of cases occur in the infant and young child group, as compared to the relatively smaller number occurring in adult life. Any number of cases of epidemic meningitis is too many, but when one considers the whole population, the actual number of cases is very small. This I have added to Dr. McCoy's chart (indicating lower part of chart) as showing the difference between the number of clinical cases which occurred and the number of people (carriers) who harbor the meningococcus in the nasopharynx. Conditions may arise to bring the carrier rate to as high as 70 per cent. Thirty-five per cent was not uncommon in army cantonments. In civil life, the carrier rate may be 35 per cent.

Epidemic Meningitis
(Bacteriology, Immunology, Complications)

Albert J. Bell, M.D., Cincinnati, Ohio

Bacteriology.—Causative organism, the diplococcus intracellularis of Weischselbaum.

Other names—the meningococcus, *Diplococcus intracellularis meningitidis,* etc., and more modernly the *Neissera meningitidis,* because of a certain similarity with other gram-negative organisms culturally, serologically, and morphologically, such as the gonococcus, catarrhalis, and flava.

Prior to 1909, meningococcus meningitis was thought to be caused by a single strain of the meningococcus. In 1909 Dopter discovered the parameningococcus, differentiated from the meningococcus by immunologic reactions and especially by the agglutination reaction.

In 1915 Gordon and Murray classified all meningococci into four groups by means of agglutination tests. According to Flexner, the Gordon Type 1 appears to correspond with the parameningococcus of Dopter, and Type 2 with the normal, or regular, meningococcus. Types 3 and 4 appear to conform to the more common intermediates. In Nicholi's classification, his Type A corresponds to Gordon's Types 1 and 3 and his Type B to Gordon's Types 2 and 4.

Since then, this grouping has generally held, and progress has consisted in finding more and more strains and attempting to correlate them with the four groups previously mentioned. Norton and Broom[1] in the Detroit epidemic isolated ninety-five strains, sixty-two of which were obtained in pure culture from spinal fluids and thirty-three of which were of nasopharyngeal origin from case contacts, and were assigned to Group 3.

It was known prior to 1923 that the differentiation of these organisms depends upon their relation to the fermentations of sugars, agglutination, and complement fixation. Subsequent work has been in the main a refinement of details and technic.

A summary of the findings of Williams and Gosling,[2] Bureau of Laboratories, Department of Health, New York City, will be instructive.

1. In cases of purulent meningitis, stained spreads are helpful, but they are unreliable for demonstrating the causal organism; that is, cultures are the only

*McCoy, George W.: Epidemic Meningitis, Association for Research in Mental and Nervous Diseases, Vol. XII of a Series of Research Publications.

reliable method. In tuberculous meningitis, on the contrary, by following strictly a special technic in preparing the spread, a large percentage of trustworthy results have been obtained.

2. Adequate cultural methods made early in the disease have been shown to demonstrate rapidly and accurately the causal organism in the great majority of cases.

3. By these methods it has been found that the meningococcus is no more difficult to isolate than other organisms, and it is a comparatively easy matter to grow the tubercle bacillus.

4. The slide agglutination test can be relied upon to identify the meningococcus as well as certain other bacteria.

5. The keeping of preliminary cultures for more than seventy-two hours has resulted in isolating interesting and unusual organisms.

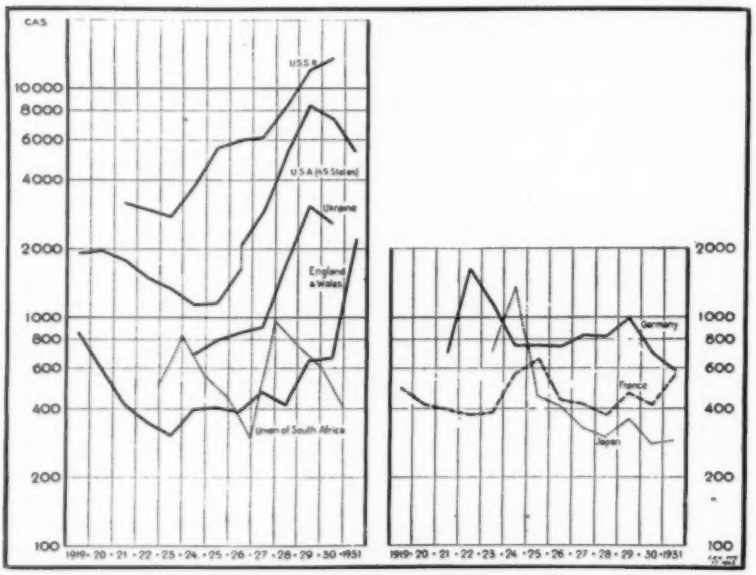

Chart 1.—Evolution of cerebrospinal meningitis (cases reported) in various countries of the world from 1919 to 1932. (Modified.)

According to Kohlbry,[3] the organism in the spinal fluid may be intra- or extracellular, according to whether the disease is mild or severe. He has found that the best culture medium is dextrose semisolid agar as prepared by Gosling. Identity of the organism may be proved by agglutination and fermentation tests.

Hasler[4] found the slide agglutination method more satisfactory than a fermentation test.

The technic for differentiating the many organisms found in the spinal fluid and nasopharynx must of necessity be omitted in this review.

Epidemiology.—Epidemic meningitis or cerebrospinal fever was recognized as an entity in 1805 when it was described by Vieusseux in Geneva, Switzerland; and McCoy[5] speculates on whether or not it had been previously overlooked, or if this was its first appearance. Sir William Osler thought it was and expressed his views

dramatically to the effect that, "In cerebrospinal fever we may be witnessing the struggle of a new disease to win a place among the great epidemics of the world." Since then it has appeared in nearly every part of the world.

A scourge to armies, epidemics may occur at long and irregular intervals, even twenty years, and may require several years to pass over a country. Sporadic cases occur yearly and their source is merely a matter of conjecture; the tracing of the source of epidemics is sometimes difficult or impossible.

The geographical distribution is not helpful as it is well known that it may jump from one country to another which is quite remote.

The line of travel is difficult to trace. In New York City in 1904 and 1905 a severe epidemic occurred while Philadelphia remained free from cases.

Let us trace as briefly as possible the world movements of epidemic meningitis for the past fifteen years as reported by the Health Section of the Secretariat, League of Nations.[6]

After the World War, when resistance might be expected to be at its lowest ebb, the incidence of the disease decreased in Western Europe until 1922 and 1923. Germany was the exception, reaching its peak in 1922 with 1,622 cases. Since then many countries, Austria, Belgium, Italy, Poland, etc., went progressively upward and reached their maxima in 1929. Similarly the United States, England, Scotland, and the Netherlands attained their high points two years later, that is, in 1931.

The United States has paralleled England, that is, a decrease after the World War until 1924, then a progressive increase; the morbidity rate was 9 per 100,000 as opposed to 6.4 in 1917.

The peak of the last epidemic wave in the United States reached the Rocky Mountain and the Pacific states, the New England states, and north central states (1929), sooner than the south central and south Atlantic states (1930).

The falling off of the disease was especially noticeable in Rocky Mountain and Pacific states, and still more so in the United States as a whole in 1932.

It is a disease of winter and spring, but cases may occur during the summer.

Race has not been considered a factor although in the recent war and in the Detroit epidemic the mortality rates were twice as high among the negroes in comparison with the white population.

Males are more often attacked than females in the proportion of 1½ to 1. This is probably due to more frequent opportunities for exposure.

TABLE FROM MCCOY

MORBIDITY RATE OF MENINGITIS PER 100,000 PERSONS IN INDIANAPOLIS, DETROIT, AND NEW YORK

AGE GROUPS	INDIANAPOLIS	DETROIT	NEW YORK
Under 1 year	281	158	194
1 to 2 years	188	150	59
5 to 9 years	106	76	35
10 to 19 years	97	51	17
20 years and over	33	19	3

Carriers: Under normal conditions, 2 to 5 per cent (Glover)[9].
Under crowded conditions, number may rise above 70 per cent.
Thirty-five per cent not uncommon in American cantonments (Rosenau).
In civilian population, noncontacts may be positive up to 35 per cent.

The age of the individual is significant, as shown in McCoy's morbidity table for Indianapolis, Detroit, and New York. In this we have seen that the greatest incidence was under one year, less so but still high under nine years, and noticeably diminished beyond this. As opposed to this, when the population affected

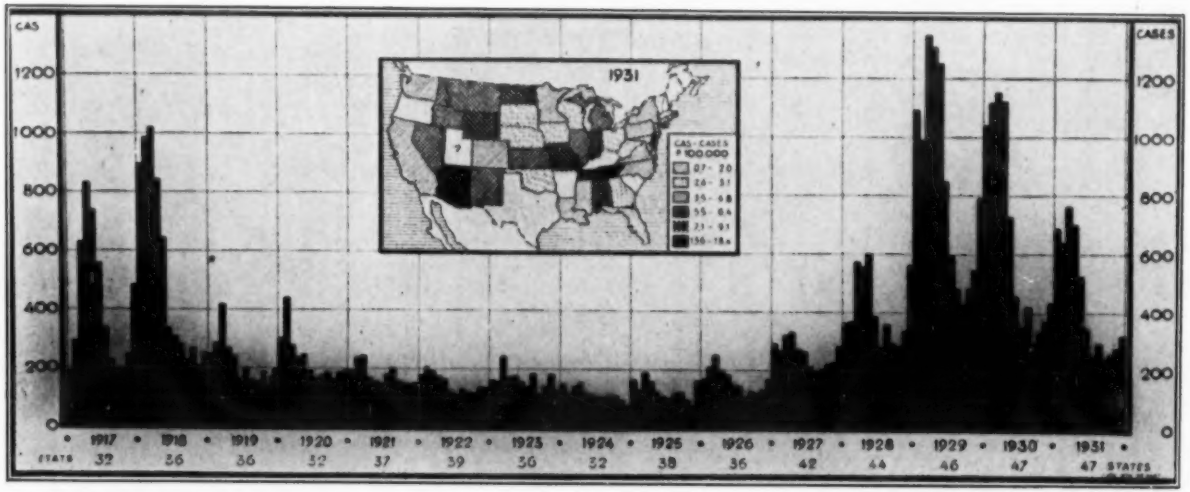

Chart 2.—Trend of cerebrospinal meningitis in the United States from 1917 to 1931 (cases reported by four-week periods).

is composed of older age groups, as in cantonments, the attack rate may be quite high, even higher than that of a definite age group in the general population.

So far as is known, none of the lower animals are carriers of this disease; man alone harbors the organism.

Vaughan says there is no doubt but that the meningococcus is carried into the body by inspired air although it may reach the nasopharynx through the mouth by means of food and drink.

The physical condition plays an important part in predisposition to this disease, and there is general agreement that overcrowding in some way plays a prominent rôle.

Although infection with the meningococcus, or rather its presence in the nasopharynx, is widespread, clinical cases are rare in comparison with other communicable diseases, according to Hedrich.[7] In the majority of instances, infection fails to progress to a frank attack; that is, while there is but slight susceptibility to the organism, the mortality of the disease is high, about 50 per cent. Expressed in other words, the death rate is high in comparison with the attack rate.

Usually only one in a family is attacked, and contacts rarely develop the disease. In the Detroit epidemic, more than one case occurred in twenty-three out of 692 houses, 3.3 per cent. There is an absence of outbreaks in schools.

The number of deaths was a trifle less than the average number of deaths from diphtheria during recent years and about the same as measles. The significance of the statement lies in the comparison between the number of cases of meningitis and those of the other two diseases, this in spite of fairly widespread use of serum. The Surgeon General's office shows 1,737 deaths out of 4,612 cases. In the Detroit epidemic, 1928 and 1929, Norton and Gordon[10] report the fatality rate in infants under one year as 84 per cent; in persons over 20 years this rate reached 64 per cent.

The carrier problem is an interesting and important one. In 1901 Albrecht and Gohn first recognized carriers of the meningococcus. Murray[8] classifies carriers into primary, or "contact" and "noncontact," and secondary, or convalescent. Glover[9] considers a high carrier rate, that is, 20 per cent, as a warning of an impending epidemic. Figures for the case-contact rate (carriers) may be found as high as 50 to 70 per cent while an attack rate of one per thousand is rare. The carrier rate of noncontact-case may be 6 per cent.

In endemic conditions the case mortality is much lower than during epidemics when the fulminating types more often occur, according to Gordon and Norton.[10]

Infection begins as a nasopharyngitis and may be limited there. Ordinarily it invades the blood, where it may also be confined or eventually reach the meninges.

The association of epidemic meningitis with poliomyelitis, epidemic encephalitis, and influenza has not been proved to be significant, as reported by Peters and Gunn.[11]

Serologically, different strains of the organism appear to be active in different epidemics, or they are not the same in epidemic or intermediate periods.

Complications.—The Eye.—Purulent conjunctivitis with abundant meningococci in the exudate may occur. It resembles gonococcic conjunctivitis, but it is not so painful, usually does not invade the cornea destructively, and responds promptly to treatment, according to Herrick.[12]

Corneal ulceration may be a complication.

Panophthalmitis may occur in from 2 to 5 per cent of the cases in the very severe types of the disease. While ordinarily only one eye is affected, both may be involved; and the outlook, as far as vision is concerned, is hopeless. Sympathetic ophthalmia never occurs, but the eye is a source of pain and toxemia, and enucleation is indicated.

In hydrocephalus, amaurosis may be observed and is of serious import. If it is caused by edema, vision may be restored. Advanced optic neuritis or atrophy is rare.

The Ear.—Otitis media of meningococcal origin may form a part of the process, and inflammation may invade destructively both middle and internal ear.

The Heart.—Myocardial degenerations are rarely ever seen.

Pericarditis may be present, either fibrinous or purulent in type; those with exudate being relieved by local serum treatment.

Dilatation of the heart, the occurrence of murmurs, and a positive blood culture may assure one of the presence of endocarditis.

The blood pressure is low during the septicemic stage in serious types of infection and is of grave import. With the onset of meningeal involvement, according to Fairley and Stewart,[13] the arterial tension usually rises, and cases in which this exceeds 120 mm. of mercury are more fatal than cases without elevation.

Internal hydrocephalus is usually accompanied by elevated blood pressure, but with the release of pressure, the blood pressure may either rise or fall. Sophian[14] has shown that a fall in blood pressure usually follows the intraspinal administration of serum.

Arthritis.—Three types have been recorded.

The first, an acute polyarthritis occurring at the onset of the disease, resembles acute rheumatic fever by involving symmetrical joints with local pain, swelling, and redness. It is probably due to hemorrhage into the synovial membranes and is usually transitory.

The second type occurs late and involves one joint, usually the knee, which becomes red and tender. The exudate is seropurulent in character and contains meningococci in about 50 per cent of the cases. The duration of this condition is long, but the prognosis is good.

The third type of arthritis is an arthralgia due to serum therapy.

Internal Hydrocephalus; Subarachnoid Block.—Continuing to quote from Herrick,[12] "The ventricular system and subarachnoid spaces form a series of channels through which the cerebrospinal fluid circulates from its principal point of origin in the choroid plexus to its principal point of absorption in the great venous sinuses. The system of channels may be blocked in any one of a number of places, most commonly about the roof of the fourth ventricle encroaching upon the foramina of Magendie and Luschka. Next in frequency the aqueduct of Sylvius is occluded."

Heightened intracranial pressure results in various pathologic changes in the brain.

Internal hydrocephalus may be acute or chronic.

Block is indicated when only a few drops of cerebrospinal fluid are seen during puncture or when it is thick, together with clinical signs of intracranial pressure.

Relapses, etc., according to Leake,[15] seldom occur after complete convalescence. "There is no case on record of a second attack of meningitis due to a different type of meningococcus than that which caused the original attack."

Metastatic foci during septicemia may complicate the picture. In some epidemics, epididymitis is seen.

Serum Reaction.—Aside from the characteristic syndrome with which we are familiar, there may be meningeal reaction lasting about twelve hours, that is, even an increase in the amount of the purulent spinal fluid.

Mixed Infections.—Councilman, Mallory, and Wright report one case in which the tubercle bacillus was seen together with the meningococcus. Nattier, Salanier, Mathews, and Fitzgerald report five cases in which the pneumococcus was superimposed upon cerebrospinal fever.

Cerebral Hemorrhage.—Montgomery[16] reported a case with the following explanation: Subependymal inflammatory lesions accompanied by necrosis are not uncommon in cerebrospinal meningitis. The necrosis of adjacent tissues in conjunction with a sclerotic artery caused it to rupture into the lateral ventricle.

Lewis[17] mentions among additional eye conditions, the occurrence of iridochor-

oiditis in an appreciable number of cases, papillitis in three cases, and blindness without visible lesions in two cases.

Cisterna Magna Pressure Syndrome.—Several cases are reported by Reuben and Chasnoff[18] and their comments are as follows:

In meningitis a syndrome (rapid pulse, rapid respiration, high or low temperature, occasionally delirium), which is probably due to pressure upon the medulla and pons by distended cisternae may develop. When this is true, a cisternal tap causes immediate improvement of the symptoms. No serum is introducted after the first tap, regardless of the character of the fluid. On return of symptoms, after a second tap is performed, if the fluid has been found to be pathogenic (organisms, etc.,), half as much serum as the amount of fluid withdrawn should be introduced; and this procedure is carried out even if the fluid can be removed by means of spinal puncture.

Certain features stand out prominently in a review of this character:

1. The manner of the spread of epidemic meningitis, which is without apparent reason and with no demonstrable or satisfactory explanation. In this respect it is similar to poliomyelitis.

2. The widespread presence of the meningococcus in the nasopharynx of healthy persons.

3. In contradistinction to this, the small number of clinical cases compared with other communicable diseases.

4. The high mortality rate, reported in some cases as high as 50 or 60 per cent and, as Osler has said, "comparable only to cholera or the plague"; this in spite of the fairly general use of serum. This may be due

   a. to an unusually virulent organism in certain epidemics;
   b. to an organism of different type from that in the serum used; or
   c. to late recognition of the disease.

The hopelessness of treating or isolating all carriers is apparent. It is important, however, for the nasopharynx of as many persons, that is, likely contacts, as possible to be examined with appropriate treatment in view; also that a study be made of the organism obtained from the throats of clinical cases with reference to a serum which would be applicable to a given epidemic.

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DISCUSSION

DR. SHAW.—Dr. Bell referred to one thing which has, in particular, engaged my interest. This is the simultaneous infection of the meninges by the meningococcus and some other organism, the case cited being one in which tubercle bacilli were present in the spinal fluid along with meningococci. In a small series of meningitis cases, I have seen three in which tubercle bacilli accompanied meningococci in the fluid; the former being demonstrable by smear, guinea pig inoculation, and autopsy findings and the latter being demonstrable by smear and culture. It seems surprising that such coincident infections should occur commonly, but I believe an explanation may lie in the effect of meningococcus toxins on the blood vessel walls. No other mode of pathogenesis seems to explain satisfactorily how, from a minute original focus, meningococci are carried into the blood stream in a profusion which exceeds any other bacterial sepsis and, with almost equal ease, pass out of the circulation at the site of final localization. The fact that other organisms may, from an accessible inflammatory focus, be carried through the blood stream along with the meningococci seems to me to emphasize the significance of the toxic vascular damage which accompanies the early stages of the infection.

DR. GILBERT S. LEVY (MEMPHIS, TENN.).—I was particularly interested in the geographic distribution of the cases inasmuch as our cases represented the majority of the cases in the outbreak of two years ago in Tennessee. It so happens that we are geographically situated as to get many cases from Mississippi and Arkansas.

The mortality during that outbreak was 45 and a fraction per cent. Strangely enough, this was the first time in sixteen years we had a severe outbreak.

Another phenomenon was the fact that the majority of cases in 1916 came from a certain part of Arkansas; in fact, the district surrounding the St. Francis River has a small community called the Panto; and in that same district a hundred cases occurred in 1916, and most of them were treated in Memphis.

In the beginning of this outbreak in 1930 and 1931, the same thing happened again, and even now we are still receiving cases. This year we have had three cases from that same neighborhood. It seems they will never be free from the carrier situation in that locality. So far as we have been able to discover, there has been no effort made to study the district and the situation.

We had a mortality rate of 23 per cent, which was in striking contrast with Indianapolis with more than 64 per cent. The mortality among the negroes was 13 per cent higher than among the whites. This is easily understood when it is known that the negroes are forced to live in small homes, sometimes four or five sleeping in the same bed. These cases were thoroughly investigated by the health department.

One other interesting fact was that we had eleven families with from two to four cases. The total number of cases for that year was approximately 300.

Dr. Bell quoted from Dr. Lewis, who made the findings, and you note he said there were three cases of sudden blindness. These three went blind overnight. He made a very thorough study of these cases. He thought there might be a reason for one of them, but he still does not know about the other two.

DR. ROBERT H. McBRIDE (SIOUX CITY, IOWA).—I wonder if the percentage of meningitis in young infants is not greater than we have thought, and the death rate also greater?

I believe a very large number of infants under six months of age, said to die of diarrhea, die of unrecognized meningitis.

I had the opportunity during the past winter of seeing a child who became ill

about three o'clock in the afternoon with malaise, headache, and temperature. At six o'clock he was very ill. About eight o'clock, the first petechiae appeared on the skin. At this time his lumbar puncture showed twenty-four cells and no organisms. A blood culture was taken. He was given intravenous treatment. The following morning he had about 12,000 cells in the spinal fluid, and the blood culture was found to be positive. He was treated in the ordinary manner. He developed blindness in one eye but never became sufficiently ill to lose consciousness or become delirious. The disease ran a mild course, but he did lose the sight of one eye completely.

I feel that they get the ophthalmitis about the same time they get the petechiae on the skin and that it is a hemorrhage in the eye, and that the organisms are carried directly there.

There is a great deal of ear trouble. Many times the child becomes completely and permanently deaf. It is interesting to know why it is such a selective thing, and why a child becomes permanently and completely deaf.

DR. GEORGE F. MUNNS (CHICAGO).—The thing that surprises me in the few cases we have had in the Children's Hospital is the comparative mildness of the disease in the early stages. It seems to me it is quite apt to fool the attending physician. I have wondered if many such cases are not missed. We have had in our wards children who presented only a slight stiffness of the neck and a mild stuporousness. We do not get to follow these cases because as soon as we find a meningococcus infection, we send the patients to the municipal contagious hospital.

DR. STANLEY GIFFEN (TOLEDO, OHIO).—I think it is very difficult to know in the case of a young child or baby who is vomiting but has no other symptoms, whether to send him to the hospital for a spinal puncture.

I had a case this winter, a three-month-old baby, who was vomiting. When I saw the child, he had no fever but was vomiting and had an acetone breath. I thought at the time it was nothing but a case of starvation, acidosis, etc. I treated the child accordingly and was much chagrined several days later to hear that the baby was still vomiting. I made a spinal puncture and found meningococci present. We treated it, but the baby died. At autopsy we found the ventricles contained thick, creamy pus.

I wonder whether or not we should puncture all vomiting babies.

DR. THOMAS J. MARSHALL (PADUCAH, KY.).—About two years ago we had an epidemic of meningitis affecting adults also. I think the first case was a boy visiting from Detroit. This occurred in December, and we continued to have meningitis along until early in the spring. We noticed when the weather was damp, there would be two or three more cases of meningitis, and when it was dry, there would be no new cases. I wonder if weather conditions do have anything to do with it.

DR. BELL.—There does not seem to be any proved connection between weather conditions and morbidity.

DR. TOOMEY.—I would like to refer to meningococcus staining. This organism is gram-negative. In the last ten years or so, a modification of the Gram stain by decolorizing with acid alcohol or acetone has been widely used. We have used this method and have finally discarded it as impractical. In a case of meningitis or suspected meningitis, where the fluid is to be stained in that fashion, a control is absolutely necessary to test the efficacy of the decolorization. It is better to adhere to the old-fashioned Gram method of decolorizing by alcohol.

I would like to ask Dr. Bell whether from his reading of the literature he can give us some information about the toxins now being described as associated with this infection.

DR. BELL.—It has been inferred that many patients die of meningitis though diagnosed as having a different disease. I think this undoubtedly occurs. If one is not expecting it, a case may be missed especially since many other conditions have meningeal symptoms, such as iliocolitis or some entity from which the child becomes very ill and comatose. I have no doubt but that there are cases of meningitis classified otherwise on the death certificate.

It has been brought out in other places, especially since the World War, that there is a high negro mortality. This susceptibility of the negro race will have to be admitted in our textbooks.

In mild cases of nasopharyngitis, it may be possible that the etiologic factor may be the meningococcus.

I am not sure that it is possible to have only a septicemia without meningitis.

If, during an epidemic of cerebrospinal meningitis, cases make us suspicious, and if we have many cases of vomiting in infants with fever, recourse should be had to a spinal puncture. It is only by being alert that we may be able to detect these conditions early enough for proper treatment to be instituted.

I am sorry I cannot elaborate on the toxins associated with this infection.

Dr. Shaw spoke of the invasion of other organisms as possibly being due to degeneration of the vascular system; I think that would be a probable and likely explanation.

Remarks on the efficacy of therapeutic serums were then made by Dr. E. B. Shaw.

The Treatment of Meningococcus Infection

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In a discussion of the treatment of meningococcus infection we must confine ourselves largely to specific therapy inasmuch as other methods of treatment have been attended with little success. The mortality of untreated meningitis is high, and such methods as spinal drainage, spinal lavage, and the intraspinal application of various antiseptics have improved the end-results but little. This paper has been designed to present the essentials of the subject to initiate round table discussions, omitting much controversial matter. Much of it is opinion advanced in the belief that it is correct but with the expectation that it may provoke sound disagreement.

The use of antimeningococcus serum was introduced during the early years of this century almost simultaneously by Jochman and by Flexner. Since this time attention has been directed to improvements in the methods of serum production and the manner of its application. One gains the impression that the serum first employed exhibited strikingly specific properties but as commercial production was undertaken during an interepidemic period therapeutic properties seem to have waned and were found sadly wanting during the extensive war-time epidemics. Reinvestigation of methods of production at this time resulted in improved specificity and therapeutic effectiveness. The period after the war has perhaps witnessed another wane in serum effectiveness, and good observers are now to be found who completely distrust its value.

Methods of Preparation.—In the production of the first serum a few clinical strains were used. The observation that there were many divergent strains led to the inclusion of more and more strains in the suspension used for immunization, until finally this procedure became almost insuperably cumbersome. It was found by Netter, Dopter, Gordon, and others that meningococci could be classified in a manner resembling pneumococci classification, into two, three, or more groups. This naturally led to the attempt to select, for the treatment of each case, a monovalent specific serum. Practically, however, this was found to be difficult because it was

found to be better to treat immediately with polyvalent serum rather than to delay for the period necessary for classification.

The method at present regarded as acceptable consists of the immunization of horses with a suspension containing representatives of each of the three recognized groups. Such a serum when carefully prepared is usually specifically effective against clinical strains. A potent serum is stated to contain bacteriolysins, agglutinins, precipitins, and bacteriotropins and to possess antiendotoxic and antiexotoxic properties difficult to evaluate. The potency of serum is usually judged by its agglutination titer against type strains but admittedly this falls far short of predicting precisely clinical effectiveness. A satisfactory agglutination titer indicates simply that the necessary strains have been included in the antigen and that an immune response has been provoked; actual therapeutic properties depend on other factors which may or may not parallel the agglutinins. The agglutination response may not be significant either to the antigenic activity of the meningococcus suspension or the therapeutic effectiveness of the serum produced. Zrodovosky has been able to produce meningitis in rabbits by the intrathecal injection of freshly isolated strains of meningococci and was unable to do so with laboratory strains. In the infected animals therapeutic effectiveness was demonstrable with serum prepared against freshly isolated strains; the use of those prepared by immunization against laboratory strains was ineffective.

There are many studies which suggest that it is desirable that serum possess antitoxic powers; even the earliest attempts at the immunization of horses included the injection of an autolysate along with the bacterial suspension. Certain clinical observations suggest the possible rôle of toxins in the pathogenesis of the disease. Recently tests, which may be of value, have been designed to determine the antitoxic activity of serum.

The final word has not yet been spoken upon the production and standardization of serum. At present this procedure is incapable of any such routinization as applies to the production of diphtheria antitoxin. Best results are secured when all procedures are constantly subjected to searching study of an investigative nature and when laboratory results are carefully checked with the clinical response.

Selection of Serum.—There is no means of selecting in advance the best serum for use in a given case. All serums are designed to be effective against any strain, and, since treatment should usually be started on the basis of information which is largely clinical and not bacteriologic, any available one may be chosen at first. It is commonly thought to be desirable finally to select from the products at hand, the serum most specific against the offending strain. This can be done at present in only two ways:

1. A growth of the organism is secured as quickly as possible from the blood, spinal fluid, or nasopharynx of the patient; a bacterial suspension prepared; and an agglutination reaction carried out with several serums. The serum which produces agglutination in the highest dilution frequently will be most active therapeutically. It must be remembered, however, that good results will be secured often with a serum of poor titer and it has been observed sometimes that one of high titer will be less effective than another giving a poor agglutination response.

Mention should be made of the fact that recently isolated strains often agglutinate poorly. We recently selected a number of strains in which various serums produced agglutination in only the lower dilutions when freshly isolated. None of these agglutinated in dilutions of over 1 to 40, and one could not be agglutinated in dilutions of more than 1 to 20, even by a very powerful type-specific serum. After these strains had been grown for several generations on laboratory media, they agglutinated with several standard serums in dilutions of from a 1 to 400 to a 1 to 4,000; only one remained inagglutinable above 1 to 400.

The evidence supplied by this test is only roughly suggestive and must not be followed blindly. Various preparations of the same manufacturer are not necessarily identical. It seems pertinent to suggest that study should be directed to the end that all serums be applicable to every case rather than that methods be developed for selecting the best serum for each individual one.

2. The clinical response in each case should, of course, be carefully watched, and, if the response to treatment is unsatisfactory, another serum may be chosen for continuance. This procedure is especially applicable to epidemics in which the same strain may be encountered throughout and in which one serum may be selected on the basis of the results in several cases.

In the individual case it is difficult in the first few days to evaluate the response to treatment. Serum produces an increase in spinal fluid cell counts, patients varying considerably in their response to this nonspecific irritating effect of serum which is altogether independent of the attendant disease. Despite subsequent recovery of the patient, organisms may be more numerous in several succeeding fluids than in the first one examined. There is, of course, no harm in changing to another serum which should at least be equally effective if one feels that the clinical response is unsatisfactory.

Method of Administration.—The plan of treatment in cerebrospinal fever must be designed with respect to the nature of the pathogenesis. The initial focus of upper respiratory infection is almost inevitably overlooked. The stage of dissemination, which follows frequently, gives a clinically recognizable picture, consisting of marked sepsis without obvious source, usually with high fever and prostration together with a rash of hemorrhagic character, which, if present, is almost pathognomonic. This is succeeded by various gradations of sepsis combined with meningitis which culminate in localization in the meninges with, in general, the spontaneous regression of the sepsis.

Cases of meningococcus sepsis, in order to be treated to forestall meningitis, must be treated on the basis of clinical signs. If these signs are not recognizable, the disease usually progresses to meningitis before it is diagnosed. All too frequently, however, meningeal localization occurs during a delay for exact bacteriologic diagnosis in the face of clinically positive symptoms.

Treatment in cases of manifest sepsis consists of the intravenous administration of serum in a dosage based roughly on 100 c.c. for an adult. Children who withstand the disease poorly and the serum well should receive a dose somewhat larger than one proportional to age and weight. Small infants may be given from 10 to 15 c.c. or more. Unless the urgency of treatment is great, precautions against serum hypersensitiveness should be employed. These consist of a careful history for general or specific protein hypersensitivness and the performance of an intracutaneous or ophthalmic test with diluted serum. It is sometimes worth while to attempt to "desensitize" the patient before intravenous injection. In many non-sensitive cases it is at least worth while to precede intravenous injection by an intramuscular initial dose of ¼ to ½ c.c., given in an extremity in such a location that, if immediate reaction occurs, a tourniquet may be placed proximal to the injection; absorption impeded; and epinephrine administered to combat the reaction. In many cases the emergency of the disease justifies intravenous therapy without any preliminary precautions. In all cases the first few centimeters injected intravenously should be given very slowly and the entire amount given as slowly as possible. It helps to reduce nonspecific, and perhaps specific, reactions if glucose solution is either mixed with the solution or given coincidentally. Epinephrine solution must always be at hand, in a loaded syringe, when any serum is given.

We have found it advantageous in giving intravenous injections of any serum to begin by injecting, by means of a gravity apparatus, a quantity of glucose, 10

per cent, in normal salt solution. As this solution is permitted to run slowly into the vein, the serum is slowly injected into the stream of glucose solution by means of a hypodermic syringe, the needle being introduced through the wall of the rubber tubing of the gravity apparatus. By this method the rate of flow of the serum is always under careful control and the admixture of glucose solution is very effective in the prevention of reaction.

The response of septic cases to intravenous treatment is much more strikingly specific than in cases of meningitis. All symptoms may regress in a few hours. This result would seem not to depend so much upon lysis and destruction of the circulating organisms as upon the neutralization of bacterial toxins which produce vascular damage and are responsible for the progress of the disease.

The repetition and frequency of dosage is not a matter of rule. A single intravenous dose is probably adequate, but it is usually repeated once or twice

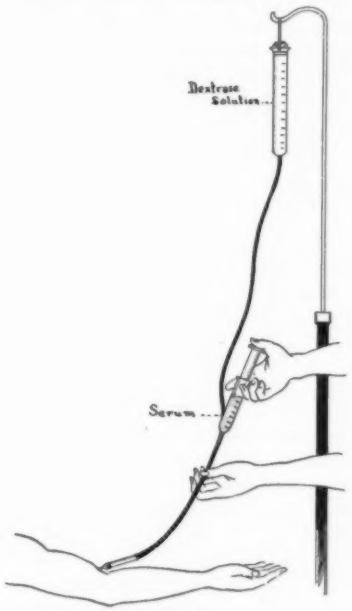


Fig. 1.

thereafter. It is not only unnecessary, but probably actually harmful, to inject serum into the spine unless there is demonstrable evidence of infection of the meninges.

Treatment of Meningitis.—If there is early involvement of the meninges, there is, because of the very nature of its pathogenesis, coincident sepsis. Many observers feel that such cases merit intravenous treatment although others, feeling that intravenous treatment in this stage is not particularly helpful and is an added risk to the patient, assert that treatment should be entirely intraspinal. In these cases of commingled sepsis and meningitis, intravenous treatment is useful if the sepsis is marked and the meningitis somewhat less so; in some of them the spinal fluid may show only a few cells and few or no organisms, and meningeal signs may be produced by vascular changes in the pia-arachnoid, which initiate the meningitis. In these very early cases all of the areas of infection may be accessible by way

of the blood stream, and serum should be given intravenously at the onset. In slightly later cases, despite the presence of an outspoken meningitis, the intensity of the disease picture may depend more on the sepsis, and intravenous treatment seems to improve the general picture greatly.

As the disease progresses, the sepsis tends to be spontaneously eradicated and the rational of intravenous treatment diminishes. However, as long as there is demonstrable evidence of persistent sepsis, it seems logical to give a single intravenous dose at the onset of treatment, but its repetition is unnecessary, particularly since intraspinal serum serves to maintain blood stream saturation.

Intraspinal treatment depends, perhaps, on different principles of serum activity than when serum is given into the blood stream. In the meninges, serum probably attacks the organisms directly rather than serving to neutralize bacterial toxins. One should endeavor to maintain intensive saturation of the subarachnoid space over a period of several days. Numerous practical points are important.

Diagnostic lumbar punctures should not be performed in a suspected case except under conditions which permit immediate administration of serum and adequate study of the fluid. If the clinical picture is sufficiently suggestive to indicate lumbar puncture and if a cloudy spinal fluid is obtained, serum should be given without delay for bacteriologic diagnosis. Proper restraint of the child in the supine position requires more skill than the puncture. A general anesthetic is seldom necessary. The use of a local anesthetic, infiltration with a 1 or 2 per cent procaine, is sometimes desirable but is usually unnecessary at subsequent treatments as it produces edema and an increased tendency to skin infection, which is undesirable. Careful antisepsis of the skin area and a strict aseptic technic are essential. The use of a miniature laparotomy sheet to drape the area is convenient. A large needle, to permit ready withdrawal of a large amount of fluid, is introduced with care to avoid drawing blood. The first few centimeters of fluid are slowly withdrawn, and as pressure falls, the fluid, if cloudy, is permitted finally to flow unimpeded. It is desirable to withdraw as much of the infected fluid as the general condition of the patient will permit, his color, pulse, and respiration being carefully watched. Usually from 30 to 40 c.c. can be secured from young infants and as much as from 50 to 80 c.c. from adults. This first treatment is the most favorable moment for the withdrawal of a large amount of fluid, which is seldom heavily purulent; and the blockage of flow, which results from the progress of the disease and from the effects of treatment, is seldom encountered.

A few drops of the fluid are allowed to flow directly from the needle into a previously warmed tube of Loeffler media (ordinary throat-culture tube) and the remainder of the fluid is sent warm to the laboratory for examination and culture.

At the end of withdrawal, an amount of serum slightly (from 5 to 10 c.c.) less than the amount of fluid withdrawn, which has been previously warmed to about body temperature, is slowly introduced without delay by means of a gravity outfit. For the same reasons which facilitate fluid withdrawal, this is the best moment for the introduction of a large amount of serum. At later treatments there has been dissemination of infection, and there is more tendency for the fluid to become more purulent and for the infection to become locally walled off. The needle should finally be quickly withdrawn and pressure applied to prevent leakage of serum into the lumbar subcutaneous tissue.

As quickly as possible, the diagnosis should be confirmed by the laboratory and a growth of the organisms secured, against which the agglutination response of various serums may be tested.

Immediate serum reactions less commonly follow intraspinal than intravenous treatment, and the seriousness of meningitis commonly justifies dispensing with elaborate precautions against them. If the history suggests sensitivity particularly,

the precautions previously referred to may be employed. Sudden shock sometimes follows treatment, resulting less from specific serum effects or from the sudden release of pressure than from increased pressure due to brain edema with consequent pressure on the medulla and interference with respiration. This is sometimes immediately fatal and is difficult to control. If it occurs, pressure should be relieved by prompt withdrawal of fluid and the patient placed head down. The administration of 5 per cent CO_2 and 95 per cent oxygen is sometimes of value in combating milder degrees of respiratory embarrassment.

Following the first treatment, the fluid usually becomes increasingly turbid due to the irritating effects of serum and, perhaps, to the stirring up of infection. Organisms are, curiously, often more numerous in fluid withdrawn at the second puncture.

We prefer to give a second treatment in twelve hours. Other observers with more experience believe a twenty-four-hour interval is more desirable. Whatever exact plan of treatment is adopted, it should be the reverse of the common practice of treating cautiously at first and heroically later. It is much better to treat most energetically at the very onset. Our plan of treatment consists of the introduction of large amounts of serum every twelve hours for from four to six doses, then at twenty-four-hour intervals for several days. The twenty-four-hour interval may be preferable throughout. Treatment should rarely consume more than one week. For a time the patient may show signs of meningeal irritation due to serum, which may completely obscure evidences of improvement. Meanwhile serum for the continuation of treatment should be selected. The use of concentrated serum, containing more specific antibodies per unit of volume may be desired when it is possible to introduce only a small amount each time. It seems advantageous, however, to withdraw as much of the infected fluid each time as is possible and to introduce a volume of serum only slightly less.

Lyon has proposed a method, of especial use in infants, of introducing coincidentally ventricular and spinal needles, admitting serum from one as fluid is withdrawn from the other and permitting the introduction of very large amounts of serum.

As treatment progresses, it is important that, in addition to careful observation of the patient's condition, the fluid be examined for evidences of improvement. The tendency is toward undue prolongation of treatment. Not infrequently the patient shows more evidence of meningeal irritation when treatment is stopped than he presented at its initiation. Cell counts usually rise after the first treatment; in response to successful therapy they slowly fall, but after one week, because of sensitization of local tissues to serum, each treatment may cause a rise in cell count, increased meningeal irritative signs, and even rise in temperature. Definite evidence of improvement is seen in:

1. Diminution and disappearance of organisms from cultures and, especially, from smears.
2. An increase in spinal fluid reducing substance.

Examination of spinal fluid for both these factors should be carefully employed daily, and serum may be cautiously withheld after a period of intensive therapy with the disappearance of organisms and the rise of spinal fluid glucose. We have occasionally ceased treatment for a time when a few scattered organisms were still present and when glucose was low, after a satisfactory serum had been intensively employed over a period of from five to seven days; thereafter a rapidly favorable termination was seen.

When it is felt that serum may safely be withheld, the patient is thereafter watched very carefully and daily examinations of the fluid are made for cells, organisms, and the amount of reducing substances. When a good therapeutic

effect has been secured, there may ensue, following cessation of treatment, rapid improvement in the patient's condition, a rapid decrease in spinal fluid cell count, the consistent absence of organisms, and the presence of a normal amount of reducing substance.

Relapses seldom occur if this plan of early intensive therapy is employed. If they are encountered, as evidenced by increased symptoms, increased cell counts, a fall of spinal fluid reducing substance, and the reappearance of organisms, recourse must be had to a resumption of intensive treatment.

Alternative Methods of Treatment.—Some observers prefer to administer serum by way of the cistern. This is technically easier than lumbar puncture and permits the advantageous use of large amounts of serum. If there is much intracranial pressure, however, the cistern may be nearly obliterated and cisternal puncture becomes highly dangerous. It is difficult to see any advantage in the withdrawal of large amounts of fluid by this method over the withdrawal of similarly large amounts by lumbar puncture. This method is justifiable only when it is impossible to obtain large amounts of fluid by lumbar or ventricular punctures because of local block or to the thick character of the fluid. Its necessity is obviated particularly by early and intensive therapy.

Intraventricular treatment is also sometimes a matter of necessity when block occurs, especially blocks at the external foramina such as are frequently encountered in infants in whom the disease may be very advanced before its recognition and in whom the exudate may become thick and fibrinous quickly. This method permits the use of large amounts of serum, is easy in infants with open fontanels, and is more difficult when a burr opening must be made. It is also usually obviated by intensive early treatment, the withdrawal of large amounts of fluid by the spinal route which nearly drains the ventricle, and by the introduction of large amounts of serum.

CONCLUSIONS

The treatment of meningococcus infections is a matter governed largely by clinical considerations. Treatment should usually be instituted on the basis of evidence which is entirely clinical, and during its continuance, laboratory procedures are a subsidiary, but none the less essential detail. It is particularly desirable that treatment be energetically applied from the outset and not at first timidly applied in a manner which permits the disease to progress to an extent which makes manifest the necessity for more intensive therapy at a later stage.

It seems logical that the study of serum therapy should be directed to the end that each serum be specifically effective in every case. No procedure will precisely determine the best serum for the treatment of the individual case.

DR. TOOMEY.—Dr. Shaw's remarks are now open for discussion.

DR. LEVY.—I am very much opposed to lumbar puncture in infants, children, or adults without an anesthetic. I have never been able to convince myself that an individual suffering from acute meningeal disease does not suffer pain, irrespective of the type of anesthetic used. Particularly in infants, I favor the use of 1 per cent novocaine. In older children and adults, particularly when pressed for time, the use of ethelyn gas and oxygen has been found very favorable in our hands. We have used it about two thousand times without any serious results. When there is plenty of time, I favor the use of novocaine.

With reference to the use of therapeutic serum in a rather large series of over five hundred cases, our conclusion until just recently was that no particular type of serum afforded any spectacular results. At the present time we are using an antitoxin which is made after the method of Dr. Ferry. It is too early to say so very much about it, as we have had only eleven cases since the first of the year.

I understand from Dr. Levinson they are using the same therapeutic serum here in Chicago. Eleven cases is too small a series to mention, perhaps. I have seen years when we have had a mortality rate of 80 or 85 per cent, and at no time has the rate been less than in the outbreak of 1930. With this new antitoxin, our mortality rate was 46 per cent. We have had only one death out of eleven patients thus treated. This one patient, an eight-year-old negro child, was in the hospital for just six hours.

The other patients ranged in age from eleven months to forty years. There were nine white and two negro patients.

One of the patients had chronic meningitis, having been ill for five weeks. When the child left the hospital, there was some evidence of hydroencephalitis. The child was able to sit up in its mother's lap a week later.

Six of these patients developed serum sickness. The serum has been used intravenously and intraspinally. The adult dose was from 75 to 100 c.c., and the dose for children from 25 to 40 c.c. in saline or glucose.

We have paid very little attention to desensitization of the cases of meningitis. I always feel, if there is a history suggestive of sensitization, we can incorporate a minimum of chloride in the intravenous medication.

Perhaps a report like this should not be mentioned but I think it might be well to exchange our findings and results.

DR. McBRIDE.—In a case where there are skin symptoms and other symptoms of meningitis and you feel pretty certain of a diagnosis, but the cell count is relatively normal, what is your procedure? Do you treat them intraspinally or intravenously and await the other treatment?

There is another thing I would take exception to; that is the size of the needle. I do not believe it is necessary to anesthetize the small child under three or four if you use a Luer needle with a short bevel and a small bore. It seems to me one gets very good results with it. If the injection is intraspinally, there is very much less bleeding later. Considerable hemorrhage due to the trauma of the needle occurs during the later part of the treatment, and there is less of hemorrhage with a small needle.

In regard to stopping the flow of the spinal fluid after having concluded the treatment and withdrawn the fluid when the puncture is done, the child is flexed and the vertebrae are spread apart posteriorly. Following the puncture, the child should be allowed to hyperextend the back, which he does spontaneously to close this opening between the vertebrae.

It has been my experience that the second and third punctures show more organisms and usually more cells.

DR. TOOMEY.—I quite agree with Dr. Shaw that a local anesthetic is not necessary for most cases.

I think he made a very good point when he called attention to the fact that in private practice one can forget all about bacteriologic cultures and agglutinations and determine the choice of antitoxin and the further course, as far as the patient's treatment is concerned, by the clinical benefits received.

I think we should be careful about treating patients for relapsing meningitis when they start to get serum sickness symptoms seven or eight days later, arthritis, hives, etc. We have seen patients that probably never would have recovered if the serum had not been stopped. I agree with the use of mass doses at first, later tapering off. Give large doses the first two days and then give a small amount of serum intramuscularly every other day for five or six doses. Then if there is a relapse, more serum should be given without fear of sensitivity reactions.

There is one point about which I disagree and that is desensitization. I have never seen any benefits from desensitization in any form. Some desensitization

of the individual who shows a definite type of reaction or positive history may have to be done in order to keep away from legal complications or possible suits.

As a matter of fact, in the last ten years we have finished an analysis of cases and divided them into a group that was sensitive to diphtheria antitoxin and a group that was not. We have injected both of these groups with diphtheria antitoxin and have found that more individuals who were desensitized had reactions as compared with those who were not desensitized.

DR. McBRIDE.—Do you feel that by giving a very great amount of fluid either intravenously or by mouth that the toxin in the blood stream or in the cerebrospinal fluid is diluted enough so that you will relieve the serious symptoms, such as permanent deafness? For instance, if you have a very sick child and fluids are forced very extensively, do you feel that there will be an effect upon the nerve deafness?

DR. SHAW.—No.

DR. TOOMEY.—I forgot to mention a very curious experience about this deafness. For ten years we did not have one case, and then in August, 1931, we had six cases in one month. Four of these were permanent, and two recovered in six months.

DR. McBRIDE.—I had three cases in the past winter, and I had only three previously. I would like to get some idea as to why these patients become deaf and if there is some possibility of preventing it.

DR. SHAW.—I think the reason for the deafness, and I would be interested in hearing other opinions, is not due so much to the involvement of the nerves as probable involvement of the inner ear.

DR. McBRIDE.—I had one patient who left the hospital in fairly good condition after ten days; three weeks after she was entirely convalescent, she developed complete deafness and is still completely deaf. I have never had one whose hearing made any improvement after becoming deaf.

I have been unable to contact any one giving a suggestion as to what may be done previous to the deafness to avoid it. The only thing I have tried to do is to increase the amount of fluid, hoping if that was toxic to dilute it as much as possible.

DR. SHAW.—It seems to occur in patients who seem to be progressing satisfactorily when the deafness is noticed.

I wanted to ask before closing if there wasn't any disagreement on the cisternal puncture. I do not like it.

DR. McBRIDE.—It is a very useful method in case you cannot puncture the spine, or in case you cannot get enough fluid out or enough serum in. It is somewhat dangerous.

Some one should mention the lack of symptoms in the child with open fontanels. Most of them do not have a single sign of meningitis. They will not have increased reflexes and they may not have a bulging fontanel. I feel this may be the reason we lose some cases. It does not hurt a baby to make a puncture, and we lose them because they are not diagnosed.

DR. SHAW.—I do not mean to state that I never use local anesthesia. It is sometimes wise to use a local anesthetic for the first puncture, but at succeeding ones the child's mental state usually makes it unnecessary. Repeated skin infiltration causes undesirable edema of the lumbar region and encourages skin infection. The patient who struggles violently against treatment may be given nitrous oxide and oxygen, or ether, though this is seldom necessary.

I am glad to hear of Dr. Levy's experience with this newer strongly antitoxic serum. It has been difficult experimentally to prove the existence and nature of these toxins, as a perusal of Gordon's work will show. Numerous experimental observations, however, strongly suggest the existence of exotoxins and endotoxins which are of importance in the pathogenesis and indicate the necessity for an antitoxic component of the serum, but clinical observations must supplement laboratory data in this matter. It seems that proper appreciation of the intoxication and the use of strongly antitoxic serum may be of great importance in future therapy.

In my manuscript I had "desensitization" in quotation marks and I tried to put the quotation marks into the reading. I do not know if we can truly desensitize, but there is no doubt that sensitization occurs. There is some comfort in being forewarned of the presence of serum hypersensitiveness by a cutaneous or ophthalmic test; nonspecific methods of combating reactions are of value whether or not specific desensitization is effective.

Extremely sensitive cases are a difficult problem. We have one patient so sensitive to horse emanations that the application of manure to the yard caused him to have a severe asthmatic attack. Could such a patient, by any method of desensitization, be safely treated with serum intravenously? It would at least be a hazardous undertaking.

The method Duke introduced for pollen injections is valuable. All subcutaneous or intramuscular serum, particularly initial doses, should be given into an extremity in such a location that if a reaction begins a tourniquet may be placed proximally so that absorption may be impeded. Only in emergency should serum be given intravenously without any kind of precautionary preliminary injections.

I have sometimes questioned if we do not increase the severity of late serum disease by a number of repeated small injections. It has been my observation that the urticaria, joint and gland swellings, etc., of late serum disease seem to be more troublesome in clinics in which serum is given with elaborate precautions than where serum is given with no precautions at all. Precautions are, of course, not directed toward late serum disease but are directed against immediate reactions where a fatal outcome is to be feared.

There is no doubt that an occasional patient may be rendered serum hypersensitive by continued injections of serum, although this is not invariably the case. I am reliably informed of a patient, whom I did not observe. Following prolonged treatment for meningitis, consisting of intravenous and intraspinal serum, the patient was discharged as recovered. After several weeks symptoms recurred, and he was found to have a positive blood culture. Serum was again promptly given intravenously, and after the first few minims has been injected, the patient died.

There is no doubt that many cases are overtreated. A neurosurgeon said the meningitis patients he sees seem to recover promptly when he has serum stopped. The fairly obvious answer is that neurosurgical consultants are called when cases are prolonged and doing badly and when adequate serum treatment has already been given.

As to the size of the needle: I prefer a large needle so that a large amount of fluid can be promptly drawn. The fluid is sometimes thick and full of fibrin flakes; a large needle obviates blocking and accelerates the procedure.

DR. McBRIDE.—What size. . . ?

DR. SHAW.—Much bigger than an intramuscular needle. I use one of the larger ones which accompany the usual outfits (from about size 16 to 18).

With regard to the patients with low cell counts, and the question of whether purulent fluid may be at a higher level which only appears in the lumbar spinal fluid later; we have had a number of early cases in which the cell counts have been so low that we have wondered if there was more extensive infection over the base

or in the ventricles. This question was answered in one such patient, who had been sick only a few hours and who showed slight neck stiffness and a few petechiae. Lumbar puncture showed a slightly turbid fluid containing many fibrin flakes but less than 200 cells per c.mm. She was treated intraspinally and died without warning about four hours later, apparently from pressure associated with brain edema. Autopsy showed no collections of pus anywhere but a diffuse and fairly uniform glazing of the pia-arachnoid. Organisms were first demonstrated in postmortem smears and cultures.

The frequency of treatment is a matter of disagreement. Many well-qualified observers hold that daily treatments are sufficient. Serum is absorbed in about eight hours so that it seems logical to treat at shorter intervals, especially during earlier and more florid stages of the disease.

We force fluids in most febrile illnesses, and to do so seems reasonable in this one. It is a question if the additional fluids cause increased flow of spinal fluid as much as do repeated or continuous drainage. Certainly after fluid has been withdrawn frequently for several days there seems to be a definite increase in secretory rate so that sometimes punctures are necessary for the relief of pressure.

Glucose is a valuable agent used intravenously in these cases. In addition to its nutritive and detoxifying virtues, it seems materially to help in the prevention of serum reactions.

Diagnosis and treatment are both difficult in infants. Sometimes the performance of a lumbar puncture will be suggested by the barest hint. It is essential that lumbar punctures be performed on suspicion and that treatment should be most intensive from the start. It is especially in this age group that the most insuperable complications occur.

DR. McBRIDE.—I had a similar experience in the spring. I watched the child twenty-four hours and failed to find any explanation for the illness. Routinely I made a lumbar puncture and found meningococci. I gave the intraventricular treatment, and the child recovered. I think we miss many cases in small children.

Dr. Toomey then introduced the next subject for discussion, namely, "Differential Diagnosis."

DR. SHAW.—I would like to ask a little more about meningomyelitis as you encounter it. How many cases have you seen and what relation have those cases to poliomyelitis? I would like to hear a little more about these cases.

DR. TOOMEY.—The sugar content of the spinal fluid is decreased in tuberculosis also, but you have a different clinical picture.

In answer to Dr. Shaw, we are vitally interested in infantile paralysis and have encountered this syndrome of dissociated meningoencephalitis in our studies of winter cases of poliomyelitis. We analyzed all these cases of poliomyelitis occurring between January and June. In looking over the histories of these cases, we convinced ourselves that approximately twenty-six of some thirty-odd cases might have been some form of encephalitis but not poliomyelitis.

The Board of Health statistics reported quite a few cases of poliomyelitis in the winter months. Most of these cases probably were epidemic encephalomyelitis. This year we have eight.

In a recent article in the *Journal of the American Medical Association*, McIntyre describes twenty cases of a new encephalopathy. I quite agree with him that there are a number of cases which might be characterized as acute myeloencephalitis, but I do not agree that all of the cases he describes could be so included under the new term. In this new syndrome, paralysis coming on without much warning is noted. This occurs most commonly in the early morning. The patient will have little or no disturbance of deep sensation. He will point to his

toes all right; he will locate his nose perfectly well. He will not be stuporous. He cannot distinguish the difference between hot and cold. Lumbar puncture may show no cellular increase. The fluid may be clear, but one striking thing is that even though clear it will have a 4 + globulin. Often there is a slight cellular increase, but it is very slight and usually of a lymphocytic character.

A striking thing about these individuals is a bladder paralysis at the onset and a paralysis of the lower rectum. Another striking thing is the clinical sequence. Nearly all recover and very rapidly. Their bladder functions will return in about seven days at the most; their bowel functions may recover quicker. An individual often recovers from the paralysis in twenty-four hours.

I do not see how one is justified in making a definite new entity of this condition. Hassin has made important contributions to the literature on the effects of toxins in the nervous tissue. As I remember his article, it appears to me that the pathologic results of all these toxins, as Dr. Shaw intimated, must be related and that one clinical syndrome has a little more or less severe degree of vascular reaction than another.

Hassin has indicated that it is absolutely impossible to differentiate encephalitic types of reaction that occur in nervous tissue.

I feel that McIntyre has seen cases who were poisoned with a more virulent toxin.

DR. GIFFEN.—In diagnosing tuberculous meningitis do you often find the tubercle bacilli?

DR. TOOMEY.—Perhaps we have been fortunate for we have been able to find the bacillus in the spinal fluid in the majority of our cases after a painstaking search.

The meeting was adjourned at 5:30 P.M.

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES

(CONTINUED)

The general data concerning children's hospitals in the United States and Canada were obtained from the same questionnaires and therefore, under the same conditions as the data regarding the staffs.

As many answers to this section of the questionnaire are incomplete, or indefinite, or omitted altogether, an accurate summary is hardly possible. However, the following general picture is presented.

Thirty-two of the group of thirty-five hospitals are in the United States and three in Canada. Those in the United States are located in seventeen states: California, Colorado, Illinois, Indiana, Maine, Maryland, Massachusetts, Mississippi, Michigan, Missouri, New York, Ohio, Pennsylvania, Washington, Wisconsin, Washington, D. C., and Iowa. These hospitals are in our largest cities:

1 Los Angeles	1 Akron	1 Detroit
1 San Francisco	1 Cincinnati	1 Ann Arbor
1 Denver	1 Cleveland	1 Kansas City
1 Seattle	1 Indianapolis	1 Saint Louis
1 Washington, D. C.	1 Iowa City	1 Staten Island
4 Chicago	1 Portland, Maine	1 Columbus
1 Baltimore	2 Boston	1 Pittsburgh
4 New York City	1 Philadelphia	1 Milwaukee
		1 Buffalo
Canada:		
1 Winnipeg	1 Toronto	1 Montreal

Twenty-seven of these institutions are located east of the Mississippi River and only five west of the Mississippi.

It is interesting to note at this point that, while there are only thirty-two children's hospitals, there are 6,667 registered hospitals in the United States and of these 4,021 are properly designated general hospitals. Children's hospitals are, therefore, less than 0.5 per cent of the total. The natural inference is that the general or other hospitals throughout the United States have departments for children and must take care of a large percentage of the children entering hospitals. This is correct, for the hospitals and dispensaries report of the White House Conference on Child Health and Protection shows a total of 81,055 beds available for children and about 47,939 bassinets, a combined total of 13 per cent of all hospital beds.

In four children's hospitals west of the Mississippi, there are 721 beds, a relatively small number in comparison to the population of that area. The fifth hospital failed to answer that section of the questionnaire.

The cost of buildings, without land values, of twenty-five institutions reporting, amounts to $23,779,037, an average of $951,180 per institution. Taken as a whole, the buildings are moderately new and seem to be fairly well located as to their general surroundings (such as sunlight and lack of noise) considering that these hospitals are in large cities, consequently in or near congested areas. Only five are in better class residence districts.

With the exception of three, the group represents private enterprise: one being under county control and two under municipal control.

Superintendents in charge are classified as follows:

10 male physicians	17 female registered nurses
5 male lay persons	1 female lay person

It is seen that registered nurses predominate in number.

As far as can be determined, the work done by these institutions is nearly all charity, the income from patients being negligible. Three-quarters of the general hospitals also accept children as free patients. For their maintenance, the children's hospitals derive their income from the following sources:

a. City, county, or state	(21)
b. Endowment fund	(30)
c. Private contributions	(35)
d. Community chest	(?)
e. Income from patients	(?)

Figures are not in form to show with any accuracy the amounts the group as a whole derives from each of the above sources. However, income from the endowment funds appears to be the chief source of support, with private contributions being second. City, county and state, third; community chests, fourth; with very little income from pay patients. (The precariousness of the position of the hospitals in any period of economic stress is at once evident.)

Figures are not available which give costs of maintaining these institutions for any fiscal year. The per capita costs, however, for 1932 average $4.82, which seems a reasonable figure.

The cost per patient per day varies from $1.87 to $9.21. In only two hospitals are the costs under $3.00 per day. In ten hospitals the costs are between $3.00 and $4.00. In nineteen hospitals the costs are over $4.00. In thirteen hospitals the costs are over $5.00; in nine the costs are over $6.00. In two hospitals the costs are over $7.00; in one of these the cost per day is $8.06 and in the other, $9.21 per day.

The thirty-three hospitals reporting total admissions show 98,373 patients cared for in 1932, or an average of 2,981. Again, comparing the general hospitals with our group, we note that the total admissions for 6,562 hospitals is estimated at 7,228,151; so that our group admitted only 1.36 per cent of the total hospital admissions including children and adults.

Total admissions in the respective children's hospitals for 1932 varied from 979 to 7,914. Eight hospitals had total admissions under 2,000; three had admissions under 1,000; thirteen hospitals had 3,000 or more admissions; eight had 4,000 or more admissions; five had 5,000 or more; four had 6,000 or more, and two had 7,000 admissions.

These children's hospitals admit patients from birth to sixteen years of age, the average being up to fourteen years. Twenty-one admit children over twelve years of age. In one instance, the age limit for the orthopedic department is placed at twenty-one. All admit both colored and white children.

The total bed capacity of this group is approximately 5,772, ranging from fifty to 350 beds in each institution. Twenty-nine have bed capacities of 100 or more. Twenty-one have 150 or more beds; thirteen have 200 or more beds; only four have over 250 beds, and three have over 300 beds. The general hospitals have something over one million beds.

TABLE I

	SUPT.	PER CAPITA	AGE LIMIT	TOTAL ADMISSIONS 1932	TOTAL BEDS	BASSINETS	CRIBS	BEDS
1	F-R.N.	$5.07	12	3,147	190	0	42	148
2	M-Phys.	6.58	14	4,897	154	44	30	80
3	M-Lay	6.719	21	2,982	265	18	28	119
4	F-R.N.	3.92	14	6,016	182	14	50	118
5	M-Phys.	6.21	15		63?	16	16	34
6	F-R.N.	4.78	13	4,116	264			
7	M-Phys.	5.24	15	2,744	146	18	86	22
8	M-Lay	2.57	14	7,083	357			
9	M-Phys.	3.88	16	3,582	342	10	80	232
10								
11	F-R.N.	3.04	12	474	100		40	60
12	M-Phys.	6.35	14	1,077	82	6	40	36
13	F-R.N.	6.22	12	1,371	50	3	11	36
14	F-R.N.	5.21	12	6,687	332	50	40	242
15	F-R.N.	3.12	12	6,074	240	10	90	140
16	M-Phys.	3.85	13	7,914	194	12	14	168
17	F-R.N.	1.87	16	2,500	168	12	96	60
18	F-R.N.	6.08	14	3,096				
19	F-R.N.	3.59	14	4,522	218	45	18	150
20	M-Phys.	9.21	13	2,009	200	80	50	
21	F-R.N.	3.25	7	2,778	340	60	260	20
22	F-R.N.	8.06	12	824	50	10	40	
23	F-Lay	4.68	12	2,068	109		17	92
24	M-Lay	5.12	12	828	190		30	160
25	M-Lay	5.392	15	1,998	110	0	27	83
26	M-Lay	6.01	15	2,415	226	5	40	181
27	M-Phys.	6.336	14	979	110			
28	F-R.N.	3.68	14	2,584	100	12	46	42
29	F-R.N.	4.69	12	2,496	136		55	81
30	F-R.N.	4.15	15	2,680	196		42	154
31	F-R.N.	3.69	14	1,288	132	7	18	107
32	F-R.N.	3.48	12	3,710	155		55	100
33	M-Phys.	3.23	14	3,249	236	6	40	190
34			?	?				
35	M-Phys.	3.93	14	2,885	135	16	65	54

This number of 5,772 is divided into bassinets for the newborn, cribs for infants under two years, and beds. Roughly, there are 542 bassinets, 1,506 cribs, and 3,724 beds. Ten hospitals have no bassinets for medical cases.

As nearly as can be estimated, private rooms are 445 out of the total, less than 8 per cent. Wards predominate, and possibly as high as 60 per cent of the wards are divided into cubicles. These figures naturally lack accuracy owing to their being more than one bed in private rooms, beds not in use and conversion from one type of ward into another type of ward. These hospitals are variable in the use of their ward beds; as the need arises they are converted into contagious wards, observation wards, etc.

The following departments prevail: medical, surgical, orthopedic, neurologic, otolaryngologic, and contagious.

Out of twenty hospitals, nine report special wards for medical cases; twenty out of thirty-three, special wards for surgical cases; fourteen out of thirty-two, special wards for orthopedic cases; two out of thirty-two, special wards for neurologic cases; thirteen out of thirty-two, for otolaryngologic cases; eighteen out of thirty-one, contagious departments; nineteen out of thirty-two, observation wards. Special departments may often be created as the need arises. While many hospitals have contagious departments, they are largely used for contagion developing within the hospital.

Only two of the entire group accept all types of cases; all the others exclude certain diseases, such as contagion in general, smallpox, mental, active venereal, pulmonary tuberculosis, etc.

Academy News

The fourth annual meeting of the **American Academy of Pediatrics** will be held at the Wade Park Manor Hotel, Cleveland, and the Cleveland Medical Library, June 11 and 12, 1934.

Program

Monday, June 11, 9 A.M.—Round Table Discussions

"Blood"	Dr. Thomas B. Cooley
"Acute Abdomen of Childhood"	Dr. Herbert E. Coe
"The Tonsil Question"	Dr. Isaac A. Abt
"Adolescence"	Dr. Borden S. Veeder
"Heart"	Dr. Hugh McCulloch
"Acute Infections"	Dr. John A. Toomey
"Newborn"	Dr. Arthur H. Parmelee
"Allergy"	Dr. Bela Schick

Monday Afternoon, June 11.—General Meeting, Cleveland Medical Library

President's Address

Address of Invited Guest,
Arvid Wallgren, Göteborg, Sweden (subject to be announced later).
Report of the Executive Board
Report of Secretary-Treasurer
Report of Regional Committees
Reports of Special Committees
(Reports will be presented in mimeograph form to the membership.)

Tuesday, June 12, 9 A.M.—Panel Discussions, Cleveland Medical Library

"Dental Caries" by Dr. Frederick F. Tisdall, Toronto, Ontario
"Ductless Glands" by Dr. R. G. Hoskins, Professor of Physiology, Harvard Medical School

(Assistants to be announced later.)

Tuesday Afternoon, June 12.—Round Table Discussions
(Repetition of Monday morning.)

General meetings will be held at the Cleveland Medical Library. This includes Panel Discussions on Tuesday morning. Round Table Discussions will be held at the Wade Park Manor Hotel.

Each man will be eligible for two Round Table Discussions, one on Monday morning, June 11, and one on Tuesday afternoon, June 12. No man will be assigned to the same Round Table Discussion twice. All Round Table Discussions will be limited to twenty-five members. No man will be listed for the Round Table Discussions unless his obligations to the Academy are paid in full.

Exhibits will be held on the main floor of the hotel in the ballroom. There will not only be commercial exhibits, but scientific and educational exhibits as well. Dr. Ruhräh will have an exhibit on poliomyelitis, and it is likely that one other exhibit showing state work will appear.

The Wade Park Manor Hotel is situated well out from the center of the city, overlooking a beautiful park and within five minutes' walk of the library where the general meetings will be held. It is also close to the buildings of the Medical School of the Western Reserve University. It is accessible to all automobile roads coming in from the south and east, being but one block off the main road.

The annual clinical meeting of Region III of the **American Academy of Pediatrics**, will be held at Rochester, Minnesota, October 4, and Minneapolis, October 5 and 6.

Dr. Carl H. Laws, 12 Pierrepont Street, Brooklyn, N. Y., has been appointed State Chairman for New York to replace Dr. Hugh Chaplin, who has resigned.

The **Indiana State Committee**, through its Chairman, Dr. O. N. Torian, has made the following report on activities in its state. Dr. Torian is a member of the Indiana Health Council and is Chairman of the Child Health Committee.

The state organization consists of a health council cooperating with the State Board of Health and the Indiana Medical Association. The Department of Child Health has been given over to this cooperating group to plan any program they see fit, for which they use the machinery already existing in the State Health Department and the organization of the State Medical Association.

The following projects have so far been undertaken:

1. Education of parents in child health—mothers by talks on child health by doctors. The state society has urged the doctors to be prepared for this undertaking, and health organizations have been urged to request doctors to speak. There has been a great deal more activity in this educative way since the present plan was adopted.

2. Education of doctors by pediatricians by lectures delivered before county or district medical societies. Much more of this has been done by pediatricians in this, the first year of the new organization, than ever before. There is a committee looking into this matter and letting it be known to county societies.

3. Immunization campaign against diphtheria and smallpox. This was recommended by the health council. The medical association published the advice to the doctors and urged them to vaccinate the indigent as well as those able to pay. The health board placed free vaccine for the indigent with each county medical society. There was strong objection from some sources, but in general the campaign was a decided success. Above all, Indiana doctors are beginning to see the wisdom of doing their part in public health.

4. The celebration of May Day is entirely in the hands of this cooperating body, and it is making all plans, using the county medical society as the responsible body in its county. Since all plans are formed by the central body and all advertising, instruction, etc., comes from this source, it places Child Health Day entirely in the hands of the doctors of the state.

The Indiana plan for child health is much like that of Illinois and Pennsylvania. There is this difference—Indiana doctors have complete control of the department and have official power to initiate and control all projects.

In such a scheme it will be difficult to get some county medical societies to cooperate and, as expected, some objection has been encountered here. In general the county societies have adopted the projects as proposed and have done their work well. It is believed that by continued persuasion, all will eventually see the advisability of falling in line and will realize the benefits to the profession in interesting themselves in child health.

Dr. M. K. Wylder, State Chairman for New Mexico, has made the following report for his state:

Number of square miles in state, 12,634.

Number of counties, 31.

Number of physicians practicing in each locality, showing area covered by each physician: It is impossible to answer this as most of our physicians are in the larger towns, and some are isolated 100 miles from any other doctor; consequently the area covered by physicians in this state is extremely variable. There are approximately 349 active, practicing licensed physicians in the state.

Number of graduates of reputable medical schools: All physicians licensed since 1900 have had to submit diplomas from reputable schools, so that only a few are not graduates of reputable schools. Two hundred fifty-five are from high class schools, and 94 from inferior schools.

Number of graduates having had no interneship—not known. Location of those limiting their practice to pediatrics: Albuquerque, 2; Sante Fe, 1; Clayton, 1.

Number of various child welfare organizations in the state and the type of work they are doing: In six counties, Colfax, Curry, Dona Ana, Grant, McKinley, and Santa Fe, there are county welfare organizations employing a full-time executive secretary who is a trained social worker. These workers all carry on a child welfare program. This program interests itself in all phases of children's work as it affects their social well-being, the dependent, neglected, and delinquent children, the physically or mentally handicapped, adoptions, child labor, and service to institutions caring for children, in the way of investigations before admittance to the institution and also the rehabilitation of the children in the communities when they leave the institutions. This same service is given to the counties not having trained social workers by the members of the field staff of the State Bureau of Child Welfare. The state and county offices render service to approximately four thousand children in our state each year. This does not include relief work with needy families where food, shelter, clothing, etc., is provided and where thousands of other children are directly benefited. The Bureau of Child Welfare is the only official organization, but many organizations have departments of child welfare.

Pediatric Society—none organized.

Members of the Academy and their location: Dr. Stuart W. Adler, Dr. M. K. Wylder, Albuquerque, N. M.

What the Academy is doing—nothing as yet.

Child death rate: Past ten years; last two years—New Mexico was admitted to the registration area in 1929, and records previous to this are considered not sufficiently accurate for statistical purposes. You will note that the infant death rate is calculated per 1,000 live births. Total death rate and infant death rate (under one year) are given for comparison:

	TOTAL DEATHS		INFANT DEATHS (UNDER ONE YEAR)	
YEAR	NUMBER	RATE (PER 1,000 POPULATION)	NUMBER	RATE (PER 1,000 LIVE BIRTHS)
1929	6,160	15.8	1,584	140.2
1930	6,301	16.0	1,659	138.3
1931	5,796	14.4	1,540	128.9
1932	5,712	14.0	1,393	118.2

exclusive of Indians

The following is a birth rate table. (Both birth and death statistics are exclusive of stillbirths.)

POPULATION		BIRTHS	
YEAR		NUMBER	RATE (PER 1,000 POPULATION)
1929	389,507	11,297	29.0
1930	394,863	11,996	30.4
1931	402,139	11,946	29.7
1932	409,415	11,786	28.8
1933	416,690	----	--
	exclusive of Indians		

Cases of patients dying from diphtheria: The following table shows the number of cases, the New Mexico rate and the U. S. rate:—

		RATES (PER 1,000 POPULATION)	
YEAR	NUMBER	NEW MEXICO	UNITED STATES
1929	35	9.0	--
1930	51	12.1	4.9
1931	45	11.2	5.0
1932	84	20.5	4.5

NEW MEXICO POPULATION
(1930 CENSUS)

COUNTY	TOTAL	INDIANS	EXCLUSIVE OF INDIANS
Bernalillo	45,430	1,106	44,324
Catron	3,282		3,282
Chavez	19,549		19,549
Colfax	19,157		19,157
Curry	15,809		15,809
DeBaca	2,893		2,893
Dona Ana	27,455		27,455
Eddy	15,842		15,842
Grant	19,050		19,050
Guadalupe	7,027		7,027
Harding	4,421		4,421
Hidalgo	5,023		5,023
Lea	6,144		6,144
Lincoln	7,198		7,198
Luna	6,247		6,247
McKinley	20,643	9,562	11,081
Mora	10,322		10,322
Otero	9,779	708	9,071
Quay	10,828		10,828
Rio Arriba	21,381	1,556	19,825
Roosevelt	11,109		11,109
Sandoval	11,144	2,930	8,214
San Juan	14,701	8,170	6,531
San Miguel	23,636		23,636
Santa Fe	19,567	433	19,134
Sierra	5,184		5,184
Socorro	9,611		9,611
Taos	14,394	765	13,629
Torrance	9,269		9,269
Union	11,036		11,036
Valencia	16,186	3,224	12,962
Total for State	423,317	28,454	394,863

Approximate number of children immunized against diphtheria, vaccinated, given typhoid vaccine: Records incomplete; however, in thirteen counties in the state during the past three and one-half years, approximately 11,274 children were immunized against diphtheria; 13,886 children were vaccinated against smallpox; 3,295 persons immunized against typhoid.

Approximate age—unknown.

Number followed up by the Schick test—unknown.

Activity of health agencies throughout the state: Six counties have full-time county health units; twenty-five counties have part-time health officers. The activity naturally varies in each county depending upon the personnel of the unit, the appropriation, whether there is a nurse, sanitary inspector, milk ordinance, etc.

Preschool and school health examinations: Most of the county health departments make school health examinations and probably most of them hold preschool clinics and examine the preschool child. These activities vary depending upon appropriations, school nurses, county nurses, etc. In at least 75 per cent of the counties of the state, both the school child and the preschool child are examined by the health units. The services of a public health nurse are furnished in twelve counties by the Commonwealth fund; these nurses are in counties where we have part-time health officers.

Methods of caring for children having defects in those families unable to pay: This varies; some are handled through the Bureau of Child Welfare, others through local organizations; some counties have tonsil and adenoid clinics for these children; others have dental clinics where the physicians and dentists donate their services. The American Legion, Red Cross, National Tuberculosis Association, women's clubs, Rotary Clubs, Masons, churches, and other organizations help defray the expense.

News and Notes

The annual meeting of the **South Carolina Pediatric Society** was held January 30 at Florence, South Carolina. There were about twenty-five in attendance. Dr. Alfred Shands and Dr. Chris Johnson of Duke University were guests of the Society. Dr. Shands exhibited a number of pathologic specimens in connection with his paper. Dr. J. I. Waring, the president of the Society, addressed the meeting. The officers elected are: Dr. J. P. Price, Florence, S. C., President.

Dr. William Weston, Jr., Columbia, S. C., Vice-President

Dr. L. B. Salters, Florence, S. C., Secretary and Treasurer.

The **Society for Pediatric Research** will hold its annual meeting in Atlantic City, May 1, under the presidency of Dr. Rustin McIntosh of New York.

The **American Pediatric Society** will hold its annual meeting at Grove Park Inn, Asheville, N. C., on May 3, 4, and 5, 1934, under the presidency of Dr. Charles A. Fife of Philadelphia.

Errata

Because of the number of requests for information, attention is called to a printer's error in spacing of the width-weight tables as published on pages 612, 613, 614, 615, in the article, "Determining Appropriate Weight for Body Build," by Helen B. Pryor and Herbert R. Stolz in the October, 1933, number of THE JOURNAL OF PEDIATRICS.

All odd numbered ages should be shoved down on the height scale as follows:

For girls—

Age 7 should begin at height 40 inches
Age 9 should begin at height 45 inches
Age 11 should begin at height 48 inches
Age 13 should begin at height 53 inches
Age 15 should begin at height 57 inches

Age 16 is the boys' table and does not apply to girls.

For boys—

Age 7 should begin with height 41 inches
Age 9 should begin with height 45 inches
Age 11 should begin with height 49 inches
Age 13 should begin with height 52 inches
Age 15 should begin with height 56 inches

Correct tables may be had of the author on request.

In Dr. Francis Scott Smyth's critical review, "Allergic Diseases," in the March, 1934, issue of the Journal, p. 414, the sentence beginning on line 24 should read:

"It is strange, however, that no mention was made of the work by McNair in this field, which the reviewer feels is fundamental."

Comments

A Message From the President

THE American Academy of Pediatrics is progressing; it is growing in size and strength; its aims and purposes are becoming more clearly defined, and there seems to be no doubt but that it fills, and will continue to fill, an important place in American child welfare, pediatric teaching and practice. As must be expected, there are wide differences in the activity of the Academy in the various localities. In some places it is an active going concern, plunging into the midst of the many problems which confront us as pediatrists; in others it is dormant and needs awakening. Two things are of extreme importance.

The first is that it should be our aim to include every qualified pediatrist in our ranks. This year the initiation fee has been lowered for twelve months because of the depression, which has weighed heavily on the medical profession, as it has on those in all walks of life—though perhaps a little more heavily on us. Every member should feel himself a special agent to enlarge the membership. Each one should do his part in this and not wait for some one to tell him. If the membership in your state is not yet complete, whose fault is it? Ask yourself if you have been doing your bit, and if you have not, get busy.

The second is that in each state the members of the Academy should get together and decide what needs to be accomplished and what action can be taken. If the Academy is not active in your part of the country, do your part to start the ball rolling and do not wait for some one to step on the accelerator. Unfortunately many people are not equipped with self-starters, but it is assumed that every member of the Academy is, or he would not be a member. Do not sit idly by and complain that the Academy in your state is accomplishing nothing. If it is not getting ahead, it is because you are not taking the interest that you should.

The Academy is your organization; it does not belong to the officers or the various state chairmen, but to the members as a whole and to each one as an individual. Everyone in it should feel a personal sense of responsibility and a personal pride in it and its work. Don't start out with an "if" or a "but" however much you may like to complain. If things are not right, consider yourself a committee of one to find out why they are not, and then consider yourself a committee of one to see that they are righted. Get together with your fellow members in personal conference or by mail, and get things going as they should be.

In some sections the enthusiasm is very great and many activities well under way; in others there has been a disposition to lag and await a leader. The state chairmen cannot do everything single-handed. Help them and let them know that you are ready and willing to help. Seek them and do not wait for them to come to you.

It is important that the conditions in each region and in each state be known. What might suit New Jersey very well would be entirely useless in Idaho, and so on. May I suggest a study of the following: the extent and nature of infant welfare work; the extent and quality of kindergarten work, especially free

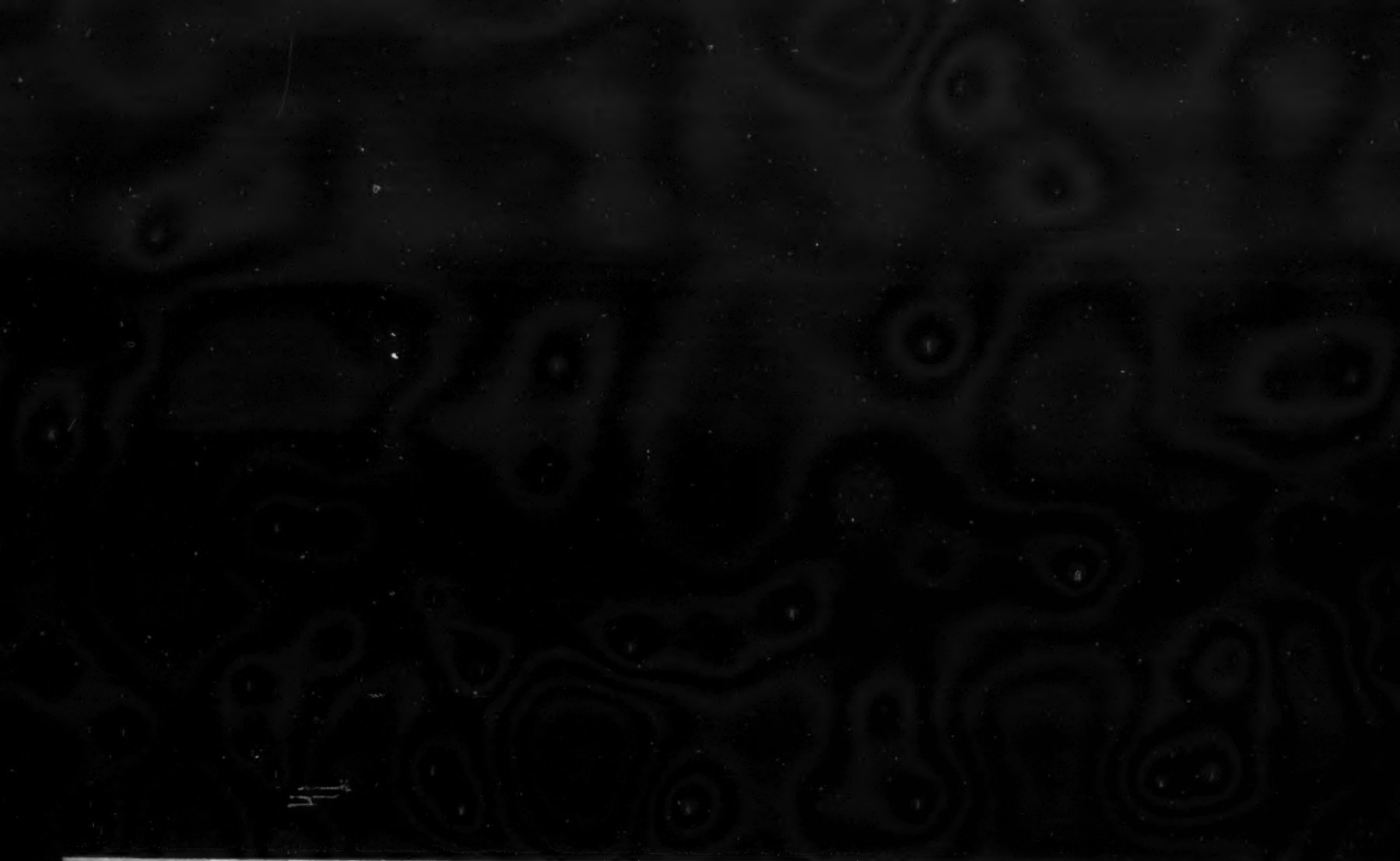
kindergarten activities; extension instruction for practitioners, particularly in rural districts; the number of hospital beds for children and the dispensary services for children, also the amount of abuse of free privileges in these; the amount of public instruction in the care of children's teeth; preventive pediatrics, nutrition and kindred topics, and whether such instruction is sending children to the free services when the parents are able and often willing to pay. Some of these subjects are being studied on a nation-wide scale, but most of the information must be supplied by the members of the Academy for their various localities. Again let me urge you to do your part without further solicitation. Only in this way can the Academy function for the benefit of all.

May every member of the executive committee, every district chairman, and every state chairman come to the Cleveland meeting with a report of progress, and let every member see to it that the reports are good ones.

JOHN RUHRÄH.

IN "News and Notes" for last month an announcement appeared regarding the American Board of Pediatrics, which is of importance to all pediatricians. The Board was formed by the three national pediatric societies, and in this sense is the agent or servant of the societies. The success of the Board will in large part depend upon the backing and support of the membership of these societies. The sole function of the Board is to certify to the competency of physicians to practice pediatrics as a specialty. Determination of competency is based on adequate training and experience. For a period of two years pediatricians of ten years or more of specialization may, on the option of the Board, be certified on record. An examination is required of all others and, after two years, of the above-mentioned group. Plans for regional examinations will be announced in the near future. The mechanism for setting up examining boards is a difficult and complicated one in view of the experience of other specialty examining boards which have been at work for a number of years.

While the immediate value of a "certificate" to the established specialist of today may seemingly be of minor importance, the necessity of establishing standards and requirements is obvious to every one. The Academy of Pediatrics is one of the sponsoring groups, and its membership should stand behind and make every effort to support the work of the Board. The Board has placed a fee of $20.00 for certification in view of the present economic conditions. The fee for three of the established boards is $50.00 and $35.00 for the fourth. No member of the Board may receive any salary, bonus, or emolument of any kind. The entire fee goes to the work of the Board including the publication and distribution of lists of licentiates.



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THE PHOTOGRAPHS TELL THE STORY

In order to determine the relative vitamin A value of plain cod liver oil and of Maltine With Cod Liver Oil, an extensive series of tests have been conducted in the Maltine laboratories which indicate that Maltine With Cod Liver Oil made a better showing than the plain cod liver oil.

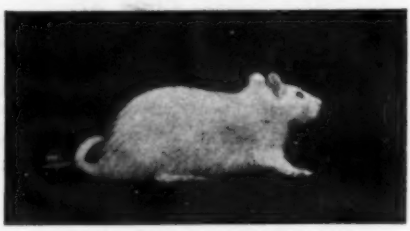
The results of these tests substantiate the statement made by a nationally known authority in his report on Maltine With Cod Liver Oil:* "In tests for vitamin A, Maltine With Cod Liver Oil gave better results than were obtained with plain cod liver oil when the latter was fed in amounts equivalent to the cod liver oil present in Maltine With Cod Liver Oil dosages." In our own tests, rat No. 2 received 4.0 mgs. of Maltine With Cod Liver Oil daily, while rat No. 1 received 0.8948 mgs. of plain cod liver oil, which is the equivalent weight of the oil in 4.0 mgs. of Maltine With Cod Liver Oil. The same cod liver oil was used in both tests.

We are convinced that the excellent showing made by Maltine With Cod Liver Oil is due to the very fine mulsified form in which the cod liver oil exists in this product. It would appear that the oil, thus finely subdivided, and in this particular form, is more completely utilized by the animal body than when plain cod liver oil is fed.

Maltine With Cod Liver Oil is biologically standardized. Seventy per cent by volume, is Maltine, a concentrated extract of the nourishing elements of malted barley, wheat and oats, rich sources of vitamins B and G. Thirty per cent by volume, is pure, vitamin-tested cod liver oil, a rich source of vitamins A and D. Administered with orange or tomato juice vitamin C is added. Biological and vitamin report on request. The Maltine Company, Est. 1875, 30 Vesey Street, New York, N. Y.

*Name on request

No. 1 (Laboratory No. 8318)
Received plain cod liver oil. Note xerophthalmic condition of eyes and poor muscular tone —almost too weak to stand. It lost 21 *grams during the* 35*-day test period.*



No. 2 (Laboratory No. 8312)
This rat received Maltine With Cod Liver Oil. *In contrast to No.* 1, *this animal exhibits bright, sparkling eyes—no signs of inflammation. It* gained 65 *grams during the* 35*-day test period.*

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